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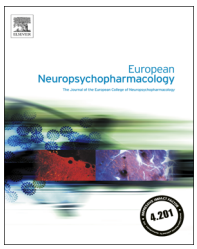

REVIEW

Learning from the past and looking to the future: Emerging perspectives for improving the treatment of psychiatric disorders

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Abstract
Modern neuropsychopharmacology commenced in the 1950s with the serendipitous discovery of first-generation antipsychotics and antidepressants which were therapeutically effective yet had marked adverse effects. Today, a broader palette of safer and better-tolerated agents is available for helping people that suffer from schizophrenia, depression and other psychiatric disorders, while complementary approaches like psychotherapy also have important roles to play in their treatment, both alone and in association with medication. Nonetheless, despite considerable efforts, current management is still only partially effective, and highly-prevalent psychiatric disorders of the brain continue to represent a huge personal and socio-economic burden. The lack of success in discovering more effective pharmacotherapy has contributed, together with many other factors, to a relative disengagement by pharmaceutical firms from neuropsychiatry. Nonetheless, interest remains high,

Abbreviations: ADHD, attention deficit hyperactivity disorder; AR, adrenergic; ASD, Autism-Spectrum Disorder; BDNF, brain derived neurotropic factor; CNV, copy number variant; COMT, catechol-o-methyltransferase; DA, Dopamine; DSM, Diagnostic and Statistical Manual; ECNP, European College of Neuropsychopharmacology; EEG, electroencephalography; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drugs Administration; GABA, gamma-aminobutyric acid; GPCR, G-protein coupled receptor; GWAS, genome-wide association study; HTS, high-throughout screening; ICD, International Classification of Disorders; iPSC, induced Pluripotent Stem Cells; MAO, monoamine oxidase; MRI, magnetic functional imaging; NA, noradrenaline; NIH, National Institute of Health; NMDA, N-methyl-D-aspartate; OCD, obsessive-compulsive disorder; PAM, positive allosteric modulator; PK/PD, pharmacokinetic/pharmacodynamic; R&D, Research and Development; SSRI, serotonin reuptake inhibitor; SGA, second-generation antipsychotic; TCA, tricyclic antidepressant; US, United States

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and partnerships are proliferating with academic centres which are increasingly integrating drug discovery and translational research into their traditional activities. This is, then, a time of transition and an opportune moment to thoroughly survey the field. Accordingly, the present paper, *first*, chronicles the discovery and development of psychotropic agents, focusing in particular on their mechanisms of action and therapeutic utility, and how problems faced were eventually overcome. *Second*, it discusses the lessons learned from past successes and failures, and how they are being applied to promote future progress. *Third*, it comprehensively surveys emerging strategies that are (1), improving our understanding of the diagnosis and classification of psychiatric disorders; (2), deepening knowledge of their underlying risk factors and pathophysiological substrates; (3), refining cellular and animal models for discovery and validation of novel therapeutic agents; (4), improving the design and outcome of clinical trials; (5), moving towards reliable biomarkers of patient subpopulations and medication efficacy and (6), promoting collaborative approaches to innovation by uniting key partners from the regulators, industry and academia to patients. Notwithstanding the challenges ahead, the many changes and ideas articulated herein provide new hope and something of a framework for progress towards the improved prevention and relief of psychiatric and other CNS disorders, an urgent mission for our Century.

Contents

1. Introduction: the challenge of improving the treatment of brain disorders

1.1. The huge personal and socio-economic burden of disorders of the brain

The two most widely-accepted and interlinked generalities concerning psychiatric disorders are their high prevalence and striking socio-economic burden on the one hand, and their inadequate current treatment on the other (Chandler, 2013; Copeland et al., 2011; Gustavsson et al., 2011; Nutt and Goodwin, 2011; Wittchen et al., 2011). As concerns their significance, several comprehensive studies, effected at the country (Chevreul et al., 2013; Clavenna et al., 2013), continental (Gustavsson et al., 2011; Wittchen et al., 2011) and world-wide (Kessler and Ustun, 2004; Murray et al., 2007) level, have now confirmed and semi-quantified the high incidence and impact of psychiatric disorders and other diseases of the brain. These surveys have underscored the enormous financial burden of psychiatric disorders to society, frequently (for example in depression, anxiety disorders and schizophrenia) due to lost employment and social support rather than the costs of treatment – with hospitalisation weighing in more heavily than medication (Gustavsson et al., 2011; Mihalopoulos et al., 2011; Skripka-Serry, 2013). Given this tremendous unmet need, even if new pharmacotherapy and complementary therapies were more expensive than generic medication, more efficacious treatment coupled to improved real-world function and socio-economic integration would unquestionably reduce the overall cost of psychiatric disorders. Arguably then, it would seem wise to persist in our efforts to better understand the causes and pathophysiological bases of psychiatric disorders, and to improve their prevention and treatment.

1.2. The current status of Research and Development (R&D) in neuropsychopharmacology

In fact, over the last two to three decades, enormous resources – public and private, academic and industrial – have been devoted to R&D for psychiatric disorders, mental health and diseases of the brain in general. There is a substantial time-lag (up to 20–25 years) between new basic discoveries (like molecular substrates of disease and potential drug targets) and availability to patients of the corresponding medication. Nonetheless, despite a handful of exceptions and improved tolerance-safety, few major and broad-based gains have been made in terms of medication *efficacy* since the introduction of first-generation psychotropic agents (Allgulander and Baldwin, 2013; Cipriani et al., 2012; Connolly and Thase, 2012; Correll et al., 2011; Leucht et al., 2013; Meltzer, 2013; Millan, 2003; 2006; Parmentier et al., 2013; Pizarro et al., 2014; Skripka-Serry, 2013; Vieta and Valentí, 2013). This lack of clear progress, together with our incomplete understanding of the origins of psychiatric disorders, has led to a certain frustration. Further, a relative disengagement of "Big Pharma" from neuroscience has also been prompted by a variety of issues: the difficult economic climate; regulatory and pricing constraints; limited duration of patent protection; risky, long and costly clinical development; competing demands of other important domains like oncology, diabetes and infective disorders; promotion of "biologicals" like antibodies and cell therapy of currently limited application to psychiatric disorders; and the (belated) realisation that sequencing the human genome will *not* provide a rapid and direct solution to enriching the pipeline for psychiatric disorders. The threat to R&D for psychiatric disorders has been highlighted in several major publications (Chandler, 2013; Cuthbert and Insel, 2010, 2013; Dean et al., 2013; Sams-Dodd, 2013; Skripka-Serry, 2013), and also by organisations such as the European College of Neuropsychopharmacology (ECNP) at a Summit meeting in 2011 (Nutt and Goodwin, 2011).

Nonetheless, as emphasised in the present article, all is not doom and gloom. Awareness and reactivity remain high, the field of Neuroscience is dynamic, highly productive and advancing rapidly, and there have been many recent and high-profile national (US) and supranational (EU) initiatives to reignite R&D for improved therapeutic control of CNS disorders (Section 9.3) (Collins et al., 2013; Dean et al., 2013; Goldman, 2012; Nutt and Goodwin, 2011; Skripka-Serry, 2013). Further, it is fallacious to believe that psychotropic drugs are generally less efficacious than other classes of medication (Broich, 2009; Leucht et al., 2012; Melander et al., 2008) – or alternative treatment strategies (Cuijpers et al., 2010; Davis et al., 2011), while challenges are being increasingly faced in essentially *all* fields of R&D for drug discovery.

Thus, the above comments should not detract from a more general and encouraging – though less visible and often neglected – current of progress in our conceptualisation, study and knowledge of psychiatric disorders since the introduction of the first wave of medication in the 1950s. While tangible gains for *patients* may not *yet* be apparent, the foundations are being laid for their future emergence, both as regards pharmacological approaches and complementary strategies like psychosocial-cognitive-behavioural and stimulation therapies, not to mention more effective programmes of prevention (Cuthbert and Insel, 2010, 2013; Kawa and Giordano, 2012; Kupfer et al., 2013; Phillips et al., 2012; Sams-Dodd, 2013; Schumann, 2014; Skripka-Serry, 2013). This note of prudent, long-term optimism provides the background to, and motor for, the present article.

1.3. Aims and organisation of this article

This would seem, then, an opportune moment to consider what we can learn from the past and also to look to the future – with a perhaps more positive (yet objective) accent than some unduly pessimistic assessments that have recently appeared elsewhere. Moreover, European Neuropsychopharmacology, the official journal of the ECNP (founded in 1987), would seem an appropriate venue for such a reflection inasmuch as this Organisation has supported R&D into disorders of the brain for nearly three decades (about half the current lifespan of neuropsychopharmacology) and will continue to do so in the future – see further below (Millan et al., 2015; Nutt and Goodwin, 2011; Wittchen et al., 2011).

The remainder of the present article, which has no pretensions to being exhaustive, is organised as follows.

First, it commences with a discussion of the serendipitous discovery of the first generation of psychotropic agents, followed by their more systematic transformation into newer classes of medication for treating schizophrenia, major depression, bipolar disorder, anxiety disorders, insomnia and Attention-Deficit Hyperactivity Disorder (ADHD) (Section 2).

Second, this account is followed by an analysis of some of the major messages to be gleaned from the successes and disappointments of the last 60 years, and their enduring relevance for neuropsychopharmacological R&D today.

Third, the following and major part of the Review focuses in more detail on the current state of affairs and prospects for progress. It evokes several factors that have made it more challenging and risky to develop new agents for improving brain health (Sections 3–9). More importantly, however, Sections 3–9 underscore a number of areas where important advances are underway that should promote future success. These include: more refined clinical characterisation of psychiatric disorders and domains of dysfunction: deeper knowledge of the pathophysiological substrates of psychiatric disorders; improved models for their experimental study; more efficient procedures of drug discovery; more flexible and better-adapted designs for clinical trials; and more intensive collaboration amongst major stakeholders in an effort to resolve current difficulties and move forward. For reasons of clarity and space, the discussion focuses mainly on antipsychotics and antidepressants, but the points raised apply to essentially all classes of medication for treating psychiatric and neurological disorders.

Finally, the article concludes by evoking certain key factors that will likely prove of central importance to future efforts to improve the treatment of psychiatric disorders and to promote brain health.

The accompanying figures and Table 1 provide an overview of the history and current use of the major classes of currently-authorised psychotropic agent, while Tables 2–4 summarise and highlight the key points raised in the discussion of Sections 3–9.

Table 1 Mechanisms of action and therapeutic utilization of psychotropic agents presented in Figures 1-5 and currently in clinical use in the EU and/or the US.

Therapeutic domain	Authorised agent	Major mechanism(s) of action	Authorised (CNS) therapeutic indications (EU and/or US)
Schizophrenia	**Chlorpromazine**	Antagonist at D1-D4, 5-HT2A/2C, histamine H1, α1-AR and muscarinic receptors.	Schizophrenia, bipolar disorder.
	Clozapine	Antagonist at D1-D4, 5-HT2A/2C, 5-HT6/7, α1-AR, α2-AR (modest), histamine H1 and muscarinic M1/M2 receptors. Partial agonist at 5-HT1A and M4 receptors. Modulator of glutamatergic and GABA transmission. 5-HT2A > D2 affinity.	Schizophrenia. Treatment-resistant psychosis, suicidality. Parkinson's disease (psychosis).
	Haloperidol	Antagonist at D1-D4, 5-HT2A (weak) and α1-AR receptors. Ligand of sigma1 sites.	Schizophrenia, mania.
	Amisulpiride	Antagonist at D2, D3 and (less potently) 5-HT_7 receptors.	Schizophrenia, depression (unspecified).
	Risperidone	Antagonist at D1-D4, 5-HT2A/2C, 5-HT7, α1-AR, α2-AR and histamine H1 receptors. 5-HT2A > D2 affinity.	Schizophrenia, bipolar disorder, Alzheimer's disease (persistent aggression). Autism (irritability, aggression).
	Sertindole	Antagonist at D1-D4, 5-HT2A/2C, 5-HT6 and α1-AR receptors. 5-HT2A > D2 affinity.	Schizophrenia.
	Olanzapine	Antagonist at D1-D4, 5-HT2A/2C, 5-HT6/7, histamine H1, α1-AR and muscarinic receptors. 5-HT2A > D2 affinity.	Schizophrenia, acute and maintenance treatment of bipolar disorder.
	Quetiapine	Antagonist at D1-D4 (weak), 5-HT2A/2C, α1-AR, histamine H1 and muscarinic receptors. 5-HT2A > D2 affinity.	Schizophrenia, bipolar disorder.
	Ziprasidone	Antagonist at D1-D4, 5-HT2A/2C, 5-HT6/7 (modest) and histamine H1 receptors. Partial agonist at 5-HT1A receptors. 5-HT2A > D2 affinity.	Schizophrenia, bipolar disorder.
	Aripiprazole	Partial agonist at D2, D3 and 5-HT_{1A} receptors. 5-HT2A and (less potent) 5-HT2C and 5-HT7 antagonist.	Schizophrenia, bipolar disorder, MDD (adjunctive), autism (irritability, paediatric), Tourette's syndrome.
	Lurasidone	Antagonist at D2, D3, 5-HT2A, 5-HT7 and α2-AR receptors. 5-HT1A partial agonist.	Schizophrenia, bipolar disorder.
Major depressive disorder	**Imipramine**	5-HT/NA reuptake inhibitor. Antagonist at α_1-AR, histamine H1 and muscarinic receptors.	MDD.
	Amitriptyline	5-HT/NA reuptake inhibitor. Antagonist at 5-HT2A/2C, α_1-AR, histamine H1 and muscarinic receptors. Na^+/Ca^{2+} ion channel blocker.	MDD, chronic pain.
	Phenelzine	Irreversible MAO inhibitor.	MDD, "atypical" depression and anxiety (unspecified).
	Clomipramine	5-HT/NA reuptake inhibitor, Antagonist at 5-HT2A/2C, α1-AR, histamine H1 and muscarinic receptors.	MDD, OCD, panic disorder.
	Bupropion	DA reuptake uptake inhibitor (modest affinity). Nicotinic receptor modulator.	MDD, smoking cessation.
	Tianeptine	Modulator of glutamatergic transmission (likely indirect).	MDD.
	Fluoxetine	5-HT reuptake inhibitor.	MDD, bipolar depression, Anxiety (unspecified), OCD, premenstrual syndrome.
	Moclobemide	Reversible MAO-A inhibitor.	MDD, social anxiety.
	Mirtazapine	Antagonist at 5-HT2A/2C, 5-HT3, α2-AR and histamine H_1 receptors.	MDD.
	Reboxetine	NA reuptake inhibitor, modest selectivity.	MDD.
	Venlafaxine	5-HT/NA reuptake inhibitor.	MDD, GAD.

Table 1 (*continued*)

Therapeutic domain	Authorised agent	Major mechanism(s) of action	Authorised (CNS) therapeutic indications (EU and/or US)
	Citalopram	5-HT reuptake inhibitor.	Depression (unspecified), panic disorder, OCD.
	Escitalopram	5-HT reuptake inhibitor.	MDD, GAD, panic disorder.
	Duloxetine	5-HT/NA reuptake inhibitor.	MDD, GAD.
	Agomelatine	Melatonin MT1 and MT2 receptor agonist, 5-HT2C receptor antagonist.	MDD.
	Vilazodone	5-HT reuptake inhibitor, 5-HT1A receptor partial agonist.	MDD.
	Vortioxetine	5-HT reuptake inhibitor, 5-HT1A/1B receptor partial agonist, 5-HT3 and 5-HT7 receptor antagonist.	MDD, GAD.
Bipolar disorder	**Lithium**	Inhibitor of inositol mono-phosphatase, and of Wnt and GSK-3β signaling. Glutamatergic and 5-HT modulator.	Bipolar disorder.
	Lamotrigine	Blocker of voltage-gated Na^+ channels, less markedly some types of Ca^{2+} channel. Leads to inhibition of glutamate release.	Bipolar disorder, epilepsy (generalized, focal and partial).
	Carbamazepine	Inactivator of Voltage-gated Na^+ (and probably Ca^{2+}) channels. Leads to inhibition of glutamate release. May enhance GABA transmission.	Bipolar disorder, epilepsy.
	Valproic acid	Promoter of GABA transmission (inhibition of GABA degradation/reuptake). Blocker of Na^+ channels. Pan-inhibitor of histone deacetylases.	Bipolar disorder, epilepsy.
Anxiety disorders and insomnia	**Chlordiazepoxide**	GABA-A receptor positive allosteric modulator.	Anxiety (unspecified), epilepsy, alcohol addiction/dependence.
	Diazepam	GABA-A receptor positive allosteric modulator.	Anxiety (unspecified, GAD), epilepsy (generalized), alcohol addiction/ dependence.
	Lorazepam	GABA-A receptor positive allosteric modulator.	Anxiety (unspecified).
	Alprazolam	GABA-A receptor allosteric modulator. High affinity.	Anxiety (unspecified), panic disorder, depression (unspecified), alcohol addiction/dependence.
	Buspirone	5-HT1A receptor partial agonist.	Anxiety (unspecified), GAD.
	Zaleplon	GABA-A receptor positive allosteric modulator.	Insomnia.
	Zopiclone	GABA-A receptor positive allosteric modulator.	Insomnia.
	Ramelteon	Agonist at melatonin MT1 and MT2 receptors.	Insomnia.
	Pregabalin	Modulator of α2δ subunit of (P/Q) voltage-dependent calcium channels. Leads to reduced glutamate and Substance P release.	GAD, epilepsy, neuropathic pain.
	Zolpidem	GABA-A receptor positive allosteric modulator.	Insomnia.
Attention deficit hyperactivity disorder	**Methylphenidate**	DA and less potent NA reuptake inhibitor.	ADHD in children and in adults.
	Amphetamine (mix of salts/ stereoisomers)	DA/NA reuptake inhibitor and releaser, Vesicular amine transporter 2 inhibitor.	ADHD, narcolepsy.
	Dextro-amphetamine (single stereoisomer)	DA/NA reuptake inhibitor and releaser, Vesicular amine transporter 2 inhibitor.	ADHD, narcolepsy.

Table 1 (*continued*)

Therapeutic domain	Authorised agent	Major mechanism(s) of action	Authorised (CNS) therapeutic indications (EU and/or US)
	Lisdexamfetamine mesylate	Same as dextroamphetamine, of which it is a pro-drug.	ADHD in children and adults.
	Atomexetine	NA reuptake inhibitor.	ADHD in children and adults.
	Clonidine	α2-AR agonist.	ADHD.
	Guanfacine	α2-AR agonist. Preference for α2A-AR subtype.	ADHD in children

The names of the drugs are international non-proprietary names. Numerous drugs have multiple mechanisms of action: only the major and therapeutically-relevant ones are indicated. Note, however, that mechanisms of action are still not fully elucidated for certain drugs. Only CNS indications are shown, and only those authorized in the US, in the entire EU, or in specific countries of the EU. See Figures 1-5 for compound dates of authorization (US if available, if not the EU), though – contra-intuitively – these dates are sometimes hard to clarify especially for the older drugs. The authorized therapeutic indications are based on the Pharmaproject and other databases and on published literature. For ADHD, children implies over 6 years of age. For more information, including off-label uses, see following citations (Connolly and Thase, 2012; Correll et al., 2011; Meltzer, 2013; Millan 2003, 2006; Parmentier et al., 2013; Pizarro et al., 2014; Vieta and Valentí, 2013; Zohar et al., 2014). Abbreviations as follows: AR, adrenergic; GAD, Generalized Anxiety Disorder; GSK, Glycogen Synthase Kinase; MAO, Monoamine Oxidase; MDD, Major depressive disorder: NA, Noradrenaline and OCD, Obsessive-Compulsive Disorder.

2. The history and evolution of pharmacotherapy for psychiatric disorders

2.1. The origins of neuropsychopharmacology

Discoveries made during the early 1950s mark the beginning of "modern" neuropsychopharmacology with the introduction of treatments for a number of psychiatric disorders (Ban, 1969; Healy, 1997; Li and Vederas, 2009; López-Muñoz and Alamo, 2009). Their clinical utility emerged from careful and sometimes unexpected observations by individual psychiatrists of the effect of novel medication in diverse patient groups. Subsequently, this initial phase evolved to one where more systematic and focused assessments were undertaken, including placebo-controlled studies, and efforts to correlate drug exposure to clinical outcome (Lasagna, 1955). Moreover, our early understanding of the actions of psychotropic drugs was facilitated by advances in chemical neuroanatomy: notably, the development of methods for measuring brain concentrations of monoamines and mapping their projections (Dahlström and Fuxe, 1964).

To better understand the current state of affairs in neuropsychopharmacology, changes underway and future progress, it is instructive to consider the past 60 years of drug discovery for psychiatric disorders. In the account below, only the major events and innovations are chronicled, such as the first drug for a specific disorder, or the introduction of a drug possessing a novel mechanism of action. Many other significant developments have taken place and numerous other useful agents have been proposed, but it is not possible to detail them all within the scope of this paper.

2.2. Antipsychotics for the treatment of schizophrenia (Figure 1, Table 1)

2.2.1. Chlorpromazine to haloperidol, the neuroleptics

Detection of the antipsychotic properties of RP4560 (Chlorpromazine) in 1952 represents a major landmark in psychiatry (Delay and Deniker, 1952). RP4560, an analogue of phenothiazine synthetised by Charpentier at the French company Rhone-Poulenc in 1950, was first investigated for its antihistaminergic properties. The French surgeon Laborit was the first to realise its potential in Neuropsychiatry while using a "lytic cocktail" of antihistaminergic drugs containing *inter alia* RP45600 with the aim of reducing post-injury shock (Laborit and Huegenard, 1951). His observations led to clinical investigations by Delay and Deniker who made the breakthrough finding that Chlorpromazine alleviated hallucinations and extinguished internal "voices" in agitated and aggressive psychotic patients (Delay et al., 1952; Delay and Deniker, 1952). These investigators also introduced the term "Neuroleptic" for this class of agent (Delay et al., 1952). Their findings were soon confirmed by several independent studies which laid the foundations for the pharmacotherapy of schizophrenia as practiced today (Ayd, 1963; Lehmann and Hanrahan, 1954; Rickels et al., 1959).

As regards mechanism of action, based on several findings it was subsequently suggested that antipsychotics may interfere with dopaminergic neurotransmission. *First*, the suppression of motor activity and the Parkinson disease-like syndrome provoked by the monoamine-depleting agent, reserpine. *Second*, the parallel observation that dopamine (DA) plays a major role in the control of extrapyramidal motor function, an observation related to the ability of the DA precursor, "L-DOPA", to alleviate Parkinson-like bradykinesia (Carlsson et al., 1958). *Third*, studies with chlorpromazine and haloperidol in rats suggested that neuroleptics block "monoaminergic receptors" and/or interfere with the release of monoamines (Carlsson and Lindqvist, 1963). Based on these arguments, together with the finding that DA-releasing drugs provoke hallucinations, Van Rossum was the first to explicitly propose "a dopaminergic hypothesis of schizophrenia" incriminating overactive dopaminergic pathways: accordingly, he posited that neuroleptics act by blocking DA receptors (Van Rossum, 1966). More direct evidence for interference by neuroleptics with dopaminergic transmission was provided a decade later by use of receptor-binding studies (Seeman et al., 1975): nanomolar concentrations of neuroleptics were shown to stereoselectively inhibit the binding of [^{3}H]-DA or

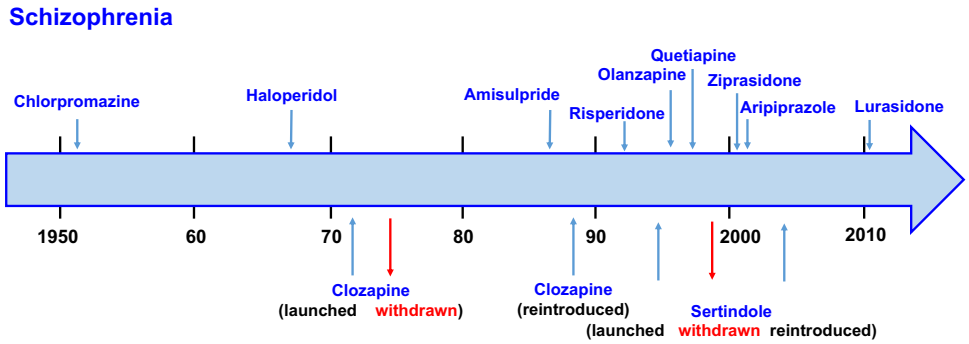

Figure 1 Schematic representation of the chronology for introduction of medication for the treatment of schizophrenia. The dates given are for approval by the FDA unless otherwise specified below. The non-propriety (WHO-approved) names of the drugs are indicated, not their commercial names which differ from region to region. Amisulpride was originally launched only in France and since then has been approved in several other countries in Europe: it is not available in the US. Clozapine was withdrawn for safety reasons (agranulocytosis) then re-introduced in light of its unique efficacy and atypical profile. Sertindole (EU) was withdrawn for reasons of cardiac safety, then re-introduced after re-assessment of its benefit-risk ratio. Many antipsychotics are also used in the treatment of bipolar disorder, and several other indications (Table 1). Not all drugs are shown, only those commented on in the text and of particular significance in terms of their mechanistic and/or therapeutic profiles.

[^{3}H]-haloperidol to D2 receptors in cerebral tissue. The DA hypothesis of schizophrenia received further support from the striking correlation between clinically-effective doses of neuroleptics and their affinities for D2 receptors (Creese et al., 1976; Seeman, 1976). No such correlation was apparent for D1 receptors, reinforcing the conviction that D2 receptors are the main target for drugs clinically effective in controlling psychosis.

Chlorpromazine was the starting point for the development of numerous drugs designed to treat schizophrenia and other psychotic states, a clinical property covered by the more general term, "antipsychotic". Of special importance was the launch of the butyrophenone, haloperidol (Janssen, Belgium), approved by the U.S. Federal Drug Administration (FDA) in 1967. Haloperidol became the prototype of drugs displaying high affinity for D2 receptors together with antipsychotic properties in both animal models and patients (Janssen et al., 1967; Leysen et al., 1992, 1994). This came at a price, however. Namely, a worryingly high tendency to elicit: *first*, extrapyramidal motor side-effects like akathisia and bradykinesia due to blockade of striatal D2 receptors; *second*, hyperprolactinaemia by antagonism of hypophyseal D2 sites inhibitory to prolactin release and *third*, in the longer term, tardive dyskinesia, probably by interfering with glutamatergic signalling in the basal ganglia (Arana, 2000; Leucht et al., 2009; Millan et al., 2000a).

2.2.2. The atypical antipsychotic, clozapine: unique clinical efficacy

A major landmark in the management of schizophrenia was the synthesis of the "atypical" agent, clozapine, by Hunziker et al. (1967). It was launched in 1971 in Europe, withdrawn in 1975 due to the risk for agranulocytosis, yet re-introduced in 1989 owing to its clinically-unique profile. Clozapine differed from haloperidol in revealing antipsychotic effects at doses that did not cause motor and endocrine side-effects (Meltzer et al., 1991). Another decisive finding was the efficacy of clozapine in a substantial proportion (about a third to a half) of patients resistant to haloperidol and other "typical" agents (Kane et al., 1988). Later on, a distinctive reduction in suicidality was confirmed across the weeks or months following onset of administration (Meltzer et al., 2003). The advantages of clozapine were suggested to reflect its *less* pronounced D2 receptor blockade compared to potent actions at a number of other sites. These included: DA D4 receptor antagonism (Lauzon and Laviolette, 2010; Millan et al., 2000a); partial agonism at 5-HT1A receptors (Millan, 2000); blockade of 5-HT2A receptors (Leysen et al., 1992; Meltzer et al., 1989) and antagonism of 5-HT2C receptors (Meltzer et al., 2012). Clozapine also was found to have relatively high affinity for 5-HT6 and 5-HT7 receptors (Roth et al., 1994; Meltzer et al., 2012). While 5-HT6 and 5-HT7 receptor blockade certainly does not fully account alone for its distinctive profile, it is interesting since. *First*, selective 5-HT6 antagonists improve cognitive function (Meffre et al., 2012; Nikiforuk, 2014). *Second*, the unusual benzamide antipsychotic, amisulpride (not marketed in the US), blocks 5-HT7 in addition to D2 receptors and may improve secondary negative symptoms and mood (Abbas et al., 2009; Leucht, 2004; Millan, 2014a, 2014b).

Finally, the high affinity of clozapine for α1-adrenergic (AR) receptors is a double-edged sword in moderating positive symptoms driven by disinhibited mesolimbic DA pathways yet provoking orthostatic hypotension (Millan et al., 2000a; Newcomer, 2005; Meltzer, 2013). Furthermore, histamine H1 and muscarinic M1 antagonism compromises cognition and provokes autonomic and metabolic side-effects (Arana, 2000; Bymaster et al., 1996; Millan et al., 2012; Newcomer, 2005).

In the wake of clozapine, the major focus was initially on reproducing its atypical profile and clinical efficacy: only later did the importance of delimiting non-motor, metabolic side-effects become a priority (Newcomer, 2005).

2.2.3. Second generation antipsychotics: the serotonin connection

Attempts to mimic the clinical profile of clozapine by focusing on the individual components of its pharmacological actions, like selective D4 receptor blockade, were fashionable for many years yet proved to be largely fruitless (Lauzon and Laviolette, 2010). The other and opposite strategy was development of second-generation antipsychotics (SGAs) acting at a palette of sites recognised by clozapine.

These drugs, approved and introduced from the mid 1990ies until virtually today, partially mimic the complex receptor-binding profile of clozapine. Notably, they all display relative marked affinities for 5-HT2A, 5-HT2C, 5-HT1A, 5-HT6 and/or 5-HT7 *vs* D2 receptors (Leysen et al., 1992; Meltzer et al., 1989, 2012; Meltzer, 2013; Millan et al., 2000a, 2000b, 2000c; Roth et al., 1994; Schotte et al., 1996). SGAs include the first of this class, risperidone, which was approved in 1994 by the FDA for the treatment of schizophrenia (Komossa et al., 2011). It became the prototypical 5-HT2A > D2 potency antipsychotic, a profile proposed to afford an "atypical"-like profile in moderating extrapyramidal motor side-effects at doses providing robust antipsychotic activity (Leysen et al.,1992; Meltzer et al., 1989; 2012; Millan et al., 2000a, 2000b, 2000c; Roth et al., 1994; Schotte et al., 1996). Risperidone was hotly pursued by olanzapine in 1996 and quetiapine in 1997, both of which conserved the 5-HT2A > D2 potency profile of risperidone and clozapine. Olanzapine is far more potent at D2 receptors than quetiapine which has disconcertingly low potency at D2 sites, yet high affinity for α1-AR receptors and histamine H1 receptors (Bymaster et al., 1996; Ishibashi et al., 2010; Leucht et al., 2013; Meltzer et al., 2012; Millan et al., 2000a; Moore et al., 1992). Ziprasidone materialised somewhat later, remained faithful to the 5-HT2A > D2 dogma yet, in contrast to its SGA forerunners, had more pronounced agonist properties at 5-HT1A receptors (Meltzer et al., 2012; Seeger et al., 1995).

However, none of these SGAs *fully* reproduce the receptor binding profile of clozapine, of which the precise, multi-modal mechanism of action still remains elusive. Correspondingly, they do not reproduce the clinical profile of clozapine which remains the Gold Standard in terms of efficacy. Further, the potent antagonist properties of SGAs at muscarinic, histamine H1 and α1-AR receptors is, as for clozapine, associated with adverse actions like sedation, weight gain, metabolic troubles and even diabetes (Arana, 2000; Leysen et al., 1994; Meltzer, 2013; Newcomer, 2005; Schotte et al., 1996). Hence, despite their undeniable clinical importance, the genuine benefits of SGAs *versus* first-generation drugs for schizophrenia is still debated (Lieberman et al., 2005; Meltzer, 2013). In any event, SGAs are broadly authorised for the treatment of bipolar disorder (Table 1) (Thase et al., 2006). As for their place in paediatric psychiatry, this is a complex issue still under investigation, as thoughtfully discussed elsewhere (Arango, 2015; Glennon et al., 2014; Rapoport, 2013).

The SGA, sertindole, justifies a brief yet highly instructive digression. Sertindole, a DA receptor antagonist, has low affinity for muscarinic and histamine H1 receptors, and was approved in Europe in 1996. However, owing to a significant risk of "QT" prolongation and hence cardiotoxicity it was withdrawn in 1998 (Lewis et al., 2005; Muscatello et al., 2014). This effect was attributed to its comparatively high affinity for so-called "hERG" (human ether-a-go-go) potassium channels in the heart (De Ponti et al., 2002; Lewis et al., 2005). The demise of Sertindole wrought havoc with many agents under development at that time for schizophrenia and other psychiatric disorders. Moreover, it provoked a sea change in the way that new ligands were screened to mitigate cardiac safety concerns. Draconian rules for elimination of compounds were enforced in screening based on more or less arbitrary cut-offs for *in vitro* affinities at hERG sites, even though the screens were not fully predictive of *in vivo* actions and an impact at hERG can be compensated for by actions at other classes of cardiac channel (De Ponti et al., 2002). Inevitably, while safety is of paramount importance and unexpected QT prolongation is thankfully a rare event today, an awful lot of babies – and indeed families (of chemical compounds) - disappeared with the bath water. Rather ironically, then, and based on a re-assessment of the complete safety data set, Sertindole was eventually reintroduced in Europe in 2002 for the treatment of schizophrenia, albeit with electrocardiographic monitoring, and mainly in patients intolerant to at least one other antipsychotic (Leucht et al., 2013; Muscatello et al., 2014).

The last multi-target agent and SGA to be launched was lurasidone (US, 2013 and EU, 2014) authorised for the treatment of both schizophrenia and bipolar disorder. The antagonist properties of lurasidone at α2-AR receptors as well as at 5-HT2A and 5-HT7 receptors have been accentuated, together with its potent partial agonist actions at 5-HT1A receptors (Ishiyama et al., 2007; Ishibashi et al., 2010). It is relatively weak at histamine H1 and muscarinic receptors. This profile may be related to cognitive improvement in animal models and to a low risk of motor side-effects. Lurasidone also shows good metabolic tolerance, but its clinical career has only just begun, so further feedback is awaited (Leucht et al., 2013; Sanford, 2013; Tarazi and Riva, 2013).

2.2.4. The D2/D3 receptor partial agonist, aripiprazole

The launch of aripiprazole in 2002 justifies emphasis. This antipsychotic is a potent antagonist at 5-HT2A receptors, as well as a partial agonist at 5-HT1A receptors yet, in contrast to SGAs, aripiprazole behaves as a partial agonist at D2 and D3 receptors. This profile permits the more precise fine-tuning and stabilisation of dopaminergic transmission compared to robust D2 receptor antagonism (Keck and McElroy, 2003; Shapiro et al., 2003). Aripiprazole must be introduced carefully to avoid undesired activation of D2 receptors, titration and appropriate dose-finding can be tricky, and it does not emulate the clinical efficacy of clozapine. Nevertheless, aripiprazole therapy is associated with a low risk for motor side-effects and, as compared to SGAs, its propensity to trigger weight gain is markedly reduced, so it must be considered a significant advance in the management of schizophrenia (Keck and McElroy, 2003; Leucht et al., 2013).

2.2.5. Lack of antipsychotic efficacy *vs* negative, neurocognitive and social cognitive symptoms

It must be emphasised that neither neuroleptics, SGAs, aripiprazole nor even clozapine display sufficient efficacy in controlling the cognitive, primary negative and social cognition/processing deficits of schizophrenia: this is important since the latter two symptom clusters are closely linked to real-world dysfunction and lack of socio-occupational integration (Foussias et al., 2014; Green, 1996; Millan et al., 2012; Millan, 2014a). Their improved treatment remains a major challenge for the future.

Moreover, as pointed out elsewhere (Millan et al., 2012; Watson et al., 2012), the D2, histamine H1 and muscarinic antagonist properties of SGAs (and clozapine) *compromise* cognitive function, questioning the wisdom of their association with putative mechanisms for improving cognitive performance, like nicotinic agonists (Geerts, 2012). This has not prevented a decade or more of such clinical trials with predictably disappointing outcomes (Millan et al., 2012).

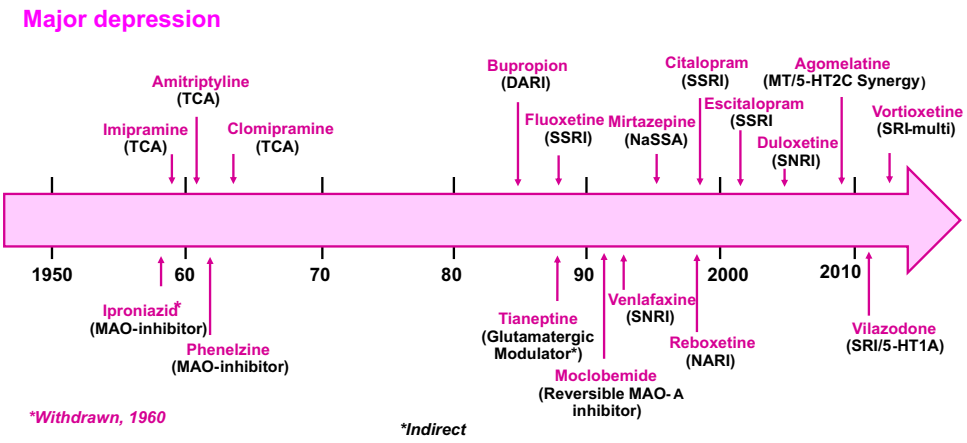

Figure 2 Schematic representation of the chronology for introduction of medication for the treatment of major depression. The dates given are for approval by the FDA unless otherwise specified below. The non-propriety, generic (WHO-approved) names of the drugs are indicated, not their commercial names which differ from region to region. Tianeptine, agomelatine and moclobemide are approved in Europe but are not available on the US market. Not all drugs are shown, only those commented on in the text and of particular significance in terms of their mechanistic and/or therapeutic profiles. Mirtazapine blocks α2-AR and 5-HT2C receptors without affecting monoamine reuptake. Note that SSRIs are also authorised for long-term treatment of anxiety states and obsessive-compulsive disorder (Table 1). Abbreviations: DARI, dopamine reuptake inhibitor; MAO, monoamine oxidase; MT, melatonin; Multi, multi-target; NARI, noradrenaline reuptake inhibitor; NaSSa; noradrenaline and specific serotonergic receptor antagonist; SNRI, 5-HT and noradrenaline reuptake inhibitor; SRI, 5-HT reuptake inhibitor; SSRI, Selective 5-HT reuptake inhibitor and TCA, tricyclic agent.

2.3. Antidepressants for the treatment of major depression (Figure 2, Table 1)

2.3.1. Tricyclic agents

In 1957, the Swiss psychiatrist, Roland Kuhn, unveiled the antidepressant properties of the iminodibenzyl, G22355 (Ciba-Geigy), an experimental compound synthetised in 1954 by Schindler and Häfliger (1954) and originally thought to be an antipsychotic (Kuhn, 1957). G22355 was later re-baptised imipramine and became the first tricyclic agent (TCA) to be approved for treatment of depression by the FDA in 1959. Imipramine was closely followed by another iminodibenzyl analogue, amitriptyline, which was also shown to be an efficacious antidepressant and approved by the FDA in 1961 (Connolly and Thase, 2012; Millan, 2006).

The findings by Kuhn were soon confirmed (Cole, 1964; Healy, 1997; Kiloh and Ball, 1961) and extended to anxiety states (Sargant and Dally, 1962). These findings prompted many studies of the potential mechanism of action of the TCAs which could not be explained at that time. In 1961, the American biochemist, Julius Axelrod, showed by use of a radioisotope technique and tritiated noradrenaline (NA) that released NA was taken up into presynaptic neurones by a specific and TCA-sensitive uptake mechanism (Axelrod et al., 1961). This led to the hypothesis that, *first*, compounds that increase brain levels of NA should possess antidepressant properties and, *second*, that depression can be attributed to a relative decrease in the activity of cerebral adrenergic neurones (Schildkraut, 1965). This "catecholamine hypothesis of affective disorders" played a pivotal role for R&D in the field of major depression for many years though, paradoxically, drugs preferentially targeting NA reuptake only crystallised much later than their serotonergic counterparts (Section 2.3.2).

Indeed, in the late 1960s, a new and competing hypotheses was formulated, "the serotonin (or 5-HT) hypothesis of depression" (Coppen, 1967), which suggested that depression is caused by low levels of serotonin in the brain. This conjecture was based on biochemical inspection of tissue from depressed patients, and on the demonstration by two independent groups of a specific 5-HT reuptake mechanism in the brain (Blackburn et al., 1967; Ross and Renyi, 1967). Determinant for the further development of antidepressants was the finding that several TCAs blocked 5-HT reuptake. These included imipramine whereas it's demethylated metabolite, the secondary amine, desipramine, preferentially interfered with *NA* uptake (Carlsson et al., 1969). This discovery triggered the proposal by the Swiss psychiatrist, Paul Kielholz, that TCAs themselves improve mood whereas their metabolites increase drive (Kielholz, 1979). A similar conjecture was made by Carlsson et al. (1969) "that blockade of 5-HT re-uptake is involved in the mood-elevating action of TCAs, whereas blockade of NA re-uptake promotes drive in the depressed patient."

Clomipramine (FDA approved, 1964) was found to be more selective in blocking 5-HT re-uptake compared to previously-launched TCAs (Carlsson et al., 1969; Millan et al., 2001). Interestingly, clomipramine is also effective in the treatment of panic disorder and especially obsessive compulsive disorder (OCD), by a mechanism poorly understood even today (Fineberg and Gale, 2005; Hall and Ogren, 1981; Pizarro et al., 2014).

2.3.2. Monoamine reuptake inhibitors: selective and multi-modal

The above-mentioned premise that an elevation in 5-HT availability enhances mood set the stage for the intensive search for 5-HT selective reuptake inhibitors (SSRIs) in the 1970s and 1980s by almost every major pharmaceutical firm worldwide (Block and Nemeroff, 2014; Connolly and Thase, 2012; Healy, 1997). Zimelidine, synthesised in 1971 and launched by the Swedish company Astra Pharmaceuticals in

1982, was the first to reach the market but withdrawn in 1983 because of adverse neurological effects. Fluoxetine (more familiar as Prozac) was developed by Eli Lilly and approved by the FDA in 1987 for major depression (Connolly and Thase, 2012; Fuller et al., 1991; Wong et al., 1990). It initiated an era enduring to this day in which fluoxetine and several others SSRIs (including fluvoxamine, paroxetine and sertraline) came to dominate the first-line treatment of major depression (Connolly and Thase, 2012; Millan, 2006). Later, SSRIs became widely-used in the control of various classes of anxiety disorder, as well as the treatment of OCD (Allgulander and Baldwin, 2013; López-Muñoz and Alamo, 2009; Millan, 2003; Parmentier et al., 2013; Wong et al., 2005).

One major advantage of SSRIs contributing to their widespread, first-line use for depression is their better safety margin compared with TCAs. This is explained by the fact that they are devoid of actions at cardiac ion channels, histaminergic H1 and muscarinic receptors. However, SSRIs elicit their own pattern of side-effects linked to excess serotonergic transmission like sexual dysfunction, nausea and, at the beginning of treatment, nervousness and anxiety (Block and Nemeroff, 2014; Millan, 2006; Stark and Hardison, 1985). In fact, fluoxetine (modestly) interacts with a number of sites other than 5-HT transporters, and the most selective of the SSRIs, citalopram (approved 1998) and its S-enantiomer, escitalopram (approved 2002), were not introduced until much later (Montgomery and Möller, 2009). Clinical results with SSRIs underpin the importance of 5-HT reuptake inhibition for their antidepressant effects, yet do not reveal which of the many (14) classes of 5-HT receptor are decisive for their actions, nor prove the 5-HT deficiency theory of depression, which is still debated to this very day (Artigas, 2013; Millan, 2006; Montgomery et al., 2007). Further, since preferential blockade of NA uptake by desipramine and the more recently-launched (1997, EU) reboxetine (Millan et al., 2001; Papakostas et al., 2008) is likewise effective in major depression (though see Eyding et al., 2010), both NA and 5-HT appear to be importance – as originally postulated by Kielholz and Carlsson (*vide supra*).

Nonetheless, as implied above, the roles of 5-HT and NA are subtly different (Millan, 2006) which prompted efforts to develop dual 5-HT/NA reuptake inhibitors, termed "SNRIs". Combined blockade of both 5-HT and NA uptake by venlafaxine (FDA approval 1997) and duloxetine (approved 2004) is associated with robust clinical efficacy. The balance of evidence suggests that "SNRIs" may have some *modest* advantages in terms of antidepressant efficacy over most SSRIs, and they may also be effective in some patients that respond poorly to SSRIs. However, not all authorities would agree on this, and the full efficacy of SNRIs may be masked since peripheral NA-mediated cardiovascular side-effects cap the maximal dose utilisable (Baldomero et al., 2005, 2014; Cipriani et al., 2012; Connolly and Thase, 2012; Millan, 2006; Millan et al., 2001; Montgomery et al., 2007; Montgomery and Möller, 2009; Rush et al., 2006). It is also worth noting that the utility of duloxetine in the control of neuropathic pain reflects (spinal) inhibition of NA rather than 5-HT reuptake – mimicking amitriptyline, though actions of the latter at Na^+ and Ca^{2+} ion channels on primary afferent nociceptive fibres may also be involved in pain relief (Micó et al., 2006; Millan, 2002).

While bupropion, introduced in 1985, blocks DA transporters, this effect is of rather modest potency and of unclear relevance to its clinical effects, not least owing to marked species differences in its metabolism (Carroll et al., 2014). Further, bupropion is not very selective for DA transporters. Actions at several nicotinic receptor subunits may also be involved in its relief of depression – and use for smoking cessation (Carroll et al., 2014; Connolly and Thase, 2012; Foley et al., 2006; Millan, 2006; Rush et al., 2006). Regrettably, recent work on triple DA/5-HT/NA reuptake inhibitors has not yet come to clinical fruition so the significance of DA reuptake blockade for relieving depression, though intuitively desirable, still remains to be proven – at least at clinically-acceptable doses devoid of any risk of abuse potential (Millan, 2006; Skolnick and Basile, 2006; Tran et al., 2012).

The lack of enhanced clinical efficacy with SSRIs relative to TCAs encouraged efforts to combine 5-HT reuptake inhibition with complementary properties (Millan, 2006, 2009). One major line of research aimed to block 5-HT1A or 5-HT1B autoreceptors in order to interrupt the feedback actions at 5-HT: it was posited that this would enhance the clinical efficacy of drugs that suppress 5-HT reuptake (Artigas, 2014; Millan et al., 2000c). Though such a mechanism *per se* never reached patients, vilazodone, which acquired US authorisation in 2011, is a 5-HT1A partial agonist/5-HT reuptake inhibitor that more powerfully elevates extracellular 5-HT levels than pure SSRIs (Connolly and Thase, 2012; Frampton, 2011; Page et al., 2002). More recently launched (2013) is vortioxetine which possesses 5-HT reuptake blocking activity plus a multi-target profile with actions at 5-HT1A, 5-HT1B, 5-HT3 and 5-HT7 receptors (Alvarez et al., 2014; Bang-Andersen et al., 2011). It is uncertain to what extent these additional sites are occupied at *clinically-used* doses in patients, but its therapeutic profile (including putative pro-cognitive properties) will be of interest to establish in clinical comparative trials (Boulenger et al., 2014; Sanchez et al., 2015).

2.3.3. Multi-target agents blocking 5-HT2C receptors: mirtazepine and agomelatine

In addition to blockade of monoamine reuptake, TCAs antagonise 5-HT2C receptors. This is important since 5-HT2C receptor blockade reinforces mesocortical DA and NA transmission and is associated with anxiolytic properties (Dekeyne et al., 2008; Millan, 2005). α2-AR receptors are inhibitory to release of DA and NA in the frontal cortex, so their blockade likewise promotes frontocortical dopaminergic and adrenergic transmission to favour mood (Millan et al., 2000b, 2000c). Interestingly, then, the "atypical" antidepressant, mirtazapine (approved by the FDA in 1996) does not interact with monoamine transporters, yet blocks both 5-HT2C and α2-AR receptors to promote frontocortical NA and DA release: as for its anxiolytic properties, they may be ascribed to 5-HT2C rather than α2-AR antagonism (Fernández et al., 2005; Millan et al., 2000b; Watanabe et al., 2011). Unfortunately, potent histamine H1 antagonism is associated with weight gain and provokes a somnolence that limits its utilisation and generally necessitates evening administration.

While selective 5-HT2C antagonists were never successfully developped, and mirtazepine possesses a purely monoaminergic mechanism of action, it is of particular interest that 5-HT2C antagonism was synergistically coupled to melatonergic agonism in the first antidepressant with a *non*-monoaminergic component of therapeutic activity: agomelatine. This agent was launched in the EU in 2009 and found to likewise possess robust

anxiolytic properties (De Bodinat et al., 2010; Guardiola-Lemaitre et al., 2014; Stein et al., 2013; Taylor et al., 2014). Agomelatine justifies a brief parenthesis from the perspective of drug discovery since it represents a good example of flexibility and reactivity. Thus, its 5-HT2C antagonist properties were not originally envisaged. Rather, they appeared in the process of screening and, in view of potential clinical utility, rather than being summarily eliminated, this activity was reinforced and carefully characterised. 5-HT2C receptor blockade: *first*, offered synergistic antidepressant properties complementary to rhythm resynchronisation; *second*, afforded supplementary anxiolytic effects and *third*, resulted in a unique pharmacological and therapeutic mechanism of action. However, an unexpected adverse impact on the liver emerged later for agomelatine. Therefore, it is important to respect contra-indications and hepatic monitoring for successful use. Collectively, the message is a rather Darwinian one of the constant need to adapt to changing circumstances in the characterisation, clinical development and therapeutic use of pharmacotherapy for patients (de Bodinat et al., 2010).

2.3.4. Other potential mechanisms of action: modulation of glutamatergic transmission

Despite the originality of agomelatine, it is interesting that it, mirtazapine and virtually all classes of antidepressant converge upon Brain-Derived Neurotrophic Factor (BDNF) and neurogenesis (comprised in depression and by chronic stress) (Duman and Voleti, 2012; Millan, 2006; Spalding et al., 2013). Nonetheless, clinical relevance for alleviation of depression remains disputed, and neither BDNF nor neurogenesis are yet to be specifically and directly harnessed by a clinically-approved antidepressant (Block and Nemeroff, 2014; Duman and Voleti, 2012).

Moreover, despite numerous intriguing routes of research such as Neurokinin-1 and Corticotrophin Releasing Factor 1 receptor antagonism, no other innovative mechanism of action has become available to treat depression. This may reflect the fact that "novel" sites were systematically exploited by highly-selective agents, which emerged to be insufficiently robust in the clinic. By contrast, coupling activity to other pharmacological properties would likely have been more effective (Section 7.1) (Connolly and Thase, 2012; Holsboer, 1999; Kehne and Cain, 2010; Millan, 2006, 2009, 2014a; Millan et al., 2010; Ratti et al., 2011).

Interestingly, tianeptine, an agent approved (1988) in the EU for treating depression, was originally suggested to act by enhancing 5-HT reuptake, but more recent work suggests that it promotes synaptic plasticity by (perhaps indirectly) modulating glutamatergic transmission (Hayley and Litteljohn, 2013; Kasper and McEwen, 2008; McEwen et al., 2010; Svenningsson and Fuchs, 2010). More recently there has been a revival of interest in the role of glutamate for management of depression (Hashimoto et al., 2013; Lapidus et al., 2013; Pilc et al., 2013). This includes blockade of metabotropic glutamatergic 2 receptors and recruitment of metabotropic glutamatergic 7 receptors (Bradley et al., 2012; Dwyer et al., 2012) but, in particular, blockade of NMDA receptors, and preferentially their NR2B subunit (Aan Het Rot et al., 2012; Fond et al., 2014; Ibrahim et al., 2012a,b). Thus the rapid onset (hours) antidepressant effect of a single dose of the non-competitive NMDA receptor antagonist, ketamine, compares favourably to the several weeks required for full efficacy of conventional agents (Aan Het Rot et al., 2012; Ballard et al., 2014; Zarate et al., 2006). This likely reflects a distinctive cellular mechanism of action, though this remains to be corroborated (Aan Het Rot et al., 2012). Whether NMDA/NR2B antagonism can be reliably, durably and safely exploited clinically without the risk of psychotomimesis or cognitive impairment is under active investigation (Fond et al., 2014; Ibrahim et al., 2012b; Zarate et al., 2006, 2013).

2.3.5. Monoamine oxidase inhibitors: irreversible to reversible

Somewhat tangential to the above story from TCAs to SSRIs to agomelatine another tale was unfolding whereby depression was treated by drugs that increased monoamine levels not by blocking their reuptake nor by promoting their release, but rather by interfering with their catabolism (Cole, 1964). This requires us to return to the 1950s.

Isoniazid, the prototype of drugs later named Monoamine Oxidase (MAO) inhibitors, was synthetised by Hoffman La Roche in 1951 in the search for more powerful drugs against tuberculosis. Isoniazid was a clinically effective antibiotic and noted to cause signs of CNS stimulation in patients. A related hydrazine derivative, iproniazid, was elaborated that revealed antidepressant properties when studied by several groups (Crane, 1957; Loomer et al., 1958), and its clinical efficacy was linked to MAO inhibition by Zeller et al. (1952). Correspondingly, as reported by Pletscher et al. (1956), rodents given ipronizid before the monoamine-depleting agent, reserpine, displayed *excitation* instead of sedation. Despite its antidepressant profile, iproniazid had high liver toxicity and the early 1960ies witnessed the development of hydrazines such as pheniprazine, an irreversible MAO inhibitor (Fagervall and Ross, 1986). This agent was launched but had to be withdrawn because of toxicity, including an interaction with foods containing tyramine, the notorious "cheese effect": this refers to the fact that irreversible MAO inhibitors protect tyramine from breakdown, thereby reinforcing its hypertensive actions. Tranylcypromine, launched 1961, is rarely used today for a similar reason. In fact, all irreversible MAO inhibitors are characterised by this potential cardiovascular side-effect, though phenelzine (launched 1961), is likewise still available to treat patients with anxious and atypical depressive symptoms (Fiedorowicz and Swartz, 2004).

Future work on MAO inhibitors was driven by two aspects: *first*, the search for safer, reversible inhibitors of MAO and, *second*, differentiation of MAO-A, which mainly metabolises 5-HT and NA, from MAO-B which preferentially metabolises DA and phenethylamines like tyramine (Lotufo-Neto et al., 1999; Priest et al., 1995). This work resulted in the launch of the reversible and well-tolerated MAO-A inhibitor moclobemide in the EU for the treatment of depression and social anxiety (Davidson, 2006; Lotufo-Neto et al., 1999). By contrast, drugs preferentially targeting MAO-B such as selegiline, (−)-deprenyl, and quite recently, rasiligine, have been oriented towards the symptomatic and possibly disease-modifying treatment of Parkinson's disease (Magyar and Szende, 2004; Youdim et al., 2001).

2.4. Agents for the treatment of bipolar disorder (Figure 3 and Table 1)

The anti-manic properties of Lithium were first described in the modern era by the Australian psychiatrist Cade in 1949 (Mitchell

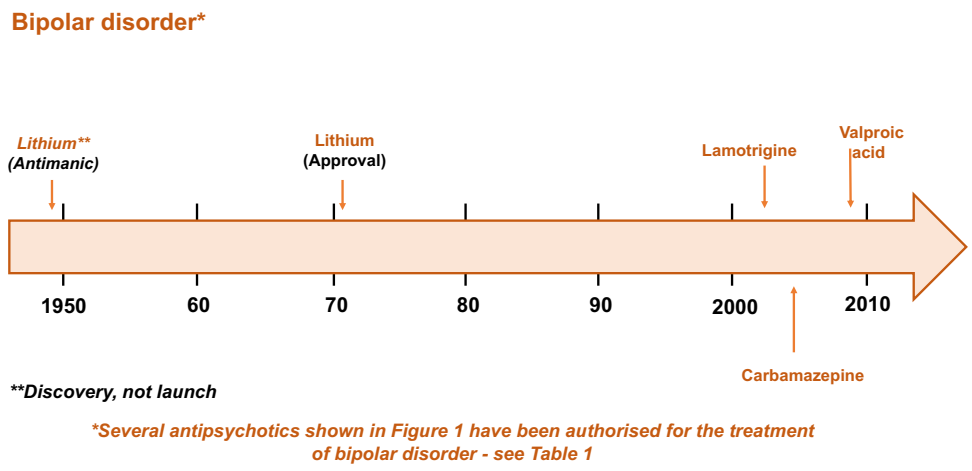

Figure 3 Schematic representation of the chronology for introduction of medication for the treatment of bipolar disorder. The dates given are for approval by the FDA. The non-propriety, generic (WHO-approved) names of the drugs are indicated, not their commercial names which differ from region to region. Drug mechanisms of action are not well understood and are outlined in the text and in Table 1. See also Table 1 for antipsychotics authorised for the treatment of treat bipolar disorder.

and Hadzi-Pavlovic, 2000). He observed that, when used as a solvent for uric acid (of which the accumulation had speculatively been linked to CNS disorders since the 1870s), Lithium protected guinea-pigs from its toxic effects, as well as inducing lethargy and tranquilisation. It took some time until he realised that this calming effect was related to Lithium itself and not to urea. After this finding, Cade (1949) started to treat psychiatric patients with Lithium and its utility to control manic episodes in bipolar patients became apparent. Later studies in the early 1950s verified Lithium's efficacy in mania and established the margin of plasma concentrations requisite for expression of its clinical properties compared to the induction of toxic side-effects (Gershon and Trautner, 1956; Noack and Trautner, 1951; Schou et al., 1954). However, the acceptance of Lithium was slow in psychiatry and almost two decades passed following its discovery until the FDA finally granted approval in 1970 for the control of bipolar disorder. Quite apart from safety concerns, one reason underlying this hesitation was the lack of insight into molecular mechanisms underlying the mood-stabilizing properties of Lithium, and this conundrum has yet to be fully resolved. Nonetheless, one prominent hypothesis suggested that Lithium inhibits the enzyme inositol mono-phosphatase: the consequent change in phosphatidylinositol metabolism may reset the sensitivity of diverse receptors and ion channels that converge onto second messengers such as Ca^{2+} and cyclic GMP (Berridge et al., 1982). More recent studies have suggested a role for cholecystokinin and a (probably indirect) inhibition of Glycogen Synthase Kinase-3β, as well as modulation of Wnt and catenin signalling, and an influence on dopaminergic, glutamatergic and serotonergic pathways (Arey et al., 2014; Duman and Voleti, 2012; Gould and Manji, 2005).

The mood-stabilizing actions of the repurposed (Section 6.3) anticonvulsants, lamotrigine (FDA approval 2003) and carbemazepine (approved 2005) appear to be complex (Calabrese et al., 1999). Lamotrigine acts at voltage-dependent Na^+ (and some classes of Ca^{2+}) channels to blunt glutamatergic transmission, and it also displays neuroprotective properties (Du et al., 2007; Ketter et al., 2003; Qiao et al., 2014). Carbamazepine stabilises the inactive state of voltage-gated Na^+ channels and has been suggested to potentiate GABAergic transmission, for example by acting at various subunits of GABA-A receptors (Granger et al., 1995; Qiao et al., 2014). It has also been suggested that they both suppress the over-activation of arachidonic acid induced signalling downstream of NMDA, D2 and other classes of receptor (Rapoport et al., 2009).

As for Valproic acid – also known as valproate – its anticonvulsant effects prompted its authorisation for the treatment of epilepsy in France in 1967 (Henry, 2003). The discovery of its antimanic and mood-stabilising effects leading to authorisation for the treatment of bipolar disorder came much later. Its actions are incompletely understood (Monti et al., 2009). They are related to blockade of Na^+ channels and increased cerebral levels of GABA, possibly due to inhibition of breakdown by GABA transaminase and interference with GABA reuptake (Löscher, 2002). This increase in GABA is also believed to contribute to its mood-stabilising and anti-manic properties (Monti et al., 2009). However, modulation of glutamatergic transmission, inhibition of arachidonic acid signalling, induction of BDNF and suppression of histone deacetylation are also implicated in the mechanisms of action of valproic acid (Arey et al., 2014; Chiu et al., 2013; Duman and Voleti, 2012; Millan, 2006, 2013; Monti et al., 2009; Rapoport et al., 2009) which await further clarification.

The last decade or so has witnessed the *en masse* reorientation of newer antipsychotics like quetiapine into bipolar disorder for mood-stabilisation, and for the control of both psychotic and (separate) manic episodes (Cipriani et al., 2011; Thase et al., 2006). However, while D2/5-HT2A receptor blockade is presumably implicated in the control of psychosis, mechanisms underlying anti-manic effects of antipsychotics are unclear, and commercial as much as pathophysiological and clinical reasoning may have encouraged this particular example of repurposing (Section 6.3). Further, despite reports that quetiapine helps alleviate depression in bipolar patients by formation of an active metabolite blocking NA reuptake (Calabrese et al., 1999; Nyberg et al., 2013), SGAs do *not* offer an acceptable solution to the chronic depression of bipolar disorder, not least in view of their metabolic and other side-effects.

The above observations suggest that there may be several ways to achieve mood-stabilisation in bipolar disorder yet, despite some interesting avenues of research like sleep and

circadian clocks (Dallaspezia and Benedetti, 2009; McCarthy and Welsh, 2012), the core mechanisms underlying mood lability remain nebulous, complicating therapeutic progress. Further, the debilitating chronic depression of bipolar disorder is pharmacologically (if not clinically) distinct from that of major (unipolar) depression in the sense that it does not respond well to conventional antidepressants – nor to mood-stabilising agents (Selle et al., 2014). A core problem for "treated" patients is that they end up being entrapped in a long-term, less fluctuating and less risk-taking yet essentially mood-suppressed state.

As starkly depicted by a comparison of Figure 3 to Figure 2, bipolar disorder has been the poor relative of major depression for far too long. This is an area of enormous need for patients and their families, and where more intensive R&D and more effective treatments are urgently awaited.

2.5. Anxiolytic agents for treating anxiety disorder and insomnia (Figure 4 and Table 1)

2.5.1. Benzodiazepines: the prototypical anxiolytics

Chlordiazepoxide was the first clinically-used benzodiazepine class to be synthesised by Leo Sternbach in 1955 (Sternbach, 1983). Experimental and clinical studies found that Chlordiazepoxide failed to affect psychotic behaviour, yet was effective in the relief of anxious states (Randall, 1961; Tobin et al., 1960) resulting in its marketing as an anxiolytic by Hoffman-LaRoche in 1960. This was followed by the launching of another benzodiazepine analogue, diazepam, in 1963, and both agents soon became highly prescribed. Unfortunately, despite their high safety margins and short-term efficacy in the treatment of various forms of anxiety – as well as seizures and ethanol withdrawal – it was later realised that extended use carries the risk of dose-escalation, physical/psychological dependence and withdrawal post-discontinuation (Lader, 2011). Further, adverse side-effects of sedation and cognitive slowing became apparent (Allgulander and Baldwin, 2013; Millan 2003; Möhler, 2012; Parmentier et al., 2013).

The generation of a diversity of benzodiazepine-related ligands in the 1970s–1980s was motivated by a desire to overcome their limitations. This second wave of agents displayed somewhat different pharmacological, pharmacokinetic and therapeutic profiles compared to classical benzodiazepines (Hevers and Lüddens, 1998; Möhler, 1983) but they were unfortunately not shed of undesirable properties like tolerance and dependence. These agents are rather numerous and can be represented by, for example, lorazepam and alprazolam, the latter a short-acting and high potency anxiolytic (Möhler, 1983; 2012; Parmentier et al., 2013).

Convincing evidence was eventually acquired that reinforcement of GABAergic transmission by binding to an allosteric site on GABA-A receptors underlies the anxiolytic properties of benzodiazepines (Millan, 2003; Möhler, 2012). Hence, two major lines of R&D were subsequently followed in renewed efforts to generate agents that retained their beneficial properties yet were devoid of adverse effects. *First*, chemically-distinct agents acting at specific allosteric sites localised on GABA-A receptors. *Second*, agents acting at specific subtypes of GABA-A receptor possessing contrasting properties and differentially distributed in the brain (Millan, 2003; Möhler, 2012). For example, agents that behaved as positive allosteric modulators (PAMs) at the $\alpha 2/3$ subtype mediating anxiolytic (and anticonvulsant) properties, yet inactive at $\alpha 1$ subtypes transducing sedation, and likewise inactive at $\alpha 5$ subtypes interfering with cognition (Atack et al., 2011; Dawson et al., 2005; Möhler et al., 2002; Millan, 2003). Differentiation between subtypes was evaluated using the properties of both affinity (high selectivity) and contrasting efficacy (agonist/PAM *vs* antagonist/negative allosteric modulator). Findings drugs that distinguish between GABA receptor subtype agents proved, in fact, highly taxing, partly due to unexpected species differences between rodents and humans. Regrettably, then, no drug reached the market despite formidable efforts in R&D (Atack et al., 2011, 2005). It is worth noting nonetheless the current evaluation of a preferential GABA-A $\alpha 2$ subtype PAM for improving cognitive function in schizophrenia (Lewis, 2012; Lewis et al., 2012).

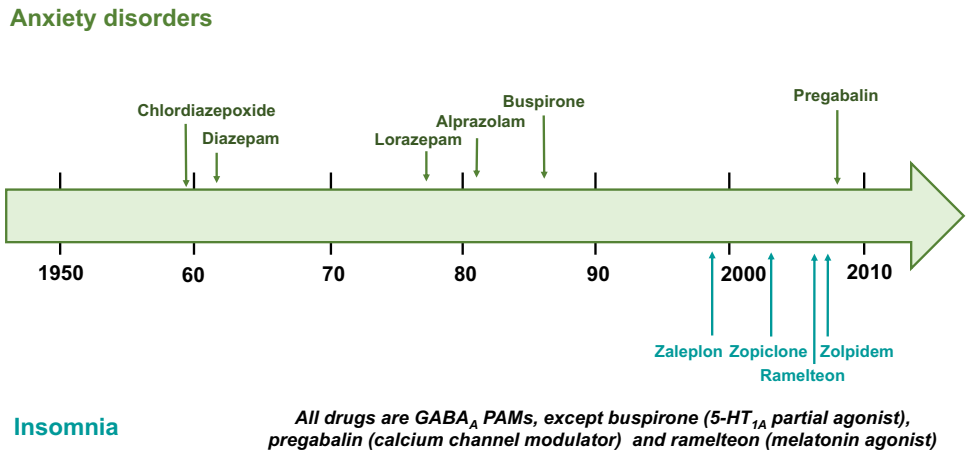

Figure 4 Schematic representation of the chronology for introduction of medication for the treatment of anxiety disorders and insomnia. The dates given are for approval by the FDA except pregabalin. The non-propriety, generic (WHO-approved) names of the drugs are indicated, not their commercial names which differ from region to region. Not all drugs are shown, only those commented on in the text and of particular significance in terms of their mechanistic and or therapeutic profiles. (See Table 1 for antidepressants used to treat anxiety disorders.) Abbreviation: PAM, positive allosteric modulator.

As concerns non-benzodiazepine classes of drug introduced for the treatment of insomnia such as zaleplon, zopiclone and zolpidem, they bind to GABA-A receptors in a manner different from classical benzodiazepines (Davies et al., 2000; Sanger, 2004). However, despite their clinically-important short-term treatment of insomnia where sleep initiation and/or sleep maintenance are compromised, they are not spared of side-effects and are far from risk-free. Indeed, prolonged use is not recommended in view of the tolerance and dependence that develops in certain individuals, by analogy with classical benzodiazepines (Parmentier et al., 2013; Sanger, 2004).

While benzodiazepines and related GABA-A receptor modulators are still widely used for the short-term control of anxious states and insomnia, longer-term management is usually undertaken with SSRIs (Allgulander and Baldwin, 2013; Millan, 2003; Parmentier et al., 2013). This can be explained by observations that their acute, 5-HT2C receptor-mediated anxiogenic actions are transformed over time (reflecting 5-HT2C receptor down-regulation) into clinically-reliable anxiolytic actions (Allgulander and Baldwin, 2013; Dekeyne et al., 2008, Millan, 2003, 2005).

2.5.2. Non-benzodiazepine agents for treating anxiety disorders and insomnia

Although pregabalin is a structural analogue of GABA, it turned out to express anxiolytic effects *via* a mechanism that differs from the benzodiazepines and the SSRIs (Baldwin and Ajel, 2007; Davidson, 2006; Parmentier et al., 2013; Strawn and Geracioti, 2007). It was approved for use in the EU in 2007. Conversely, it is not yet approved for this indication in the US, where it is authorised for the treatment of pain (Toth, 2014). The anxiolytic (and, in the dorsal horn, analgesic) effects of pregabalin reflect its occupation of synaptic terminal-localised $\alpha 2\delta$ sub-units of voltage-gated Ca^{2+} channels, thereby blunting excessive release of excitatory neurotransmitters like glutamate and substance P (Kavoussi, 2006; Owen, 2007). Clinical studies suggest advantages in comparison with benzodiazepines as concerns its low potential for abuse and withdrawal, at least after short-term use (Baldwin and Ajel, 2007; Baldwin et al., 2013; Pande et al., 2003).

In contrast to pregabalin, the azaspirone buspirone does not interact with GABA receptors. Rather this 5-HT1A partial agonist likely moderates the stress-induced release of 5-HT in the hippocampus and amygdala to blunt over-activation of post-synaptic 5-HT2C receptors (Millan et al., 2000c). Buspirone has been authorised for treatment of GAD and other anxious states in the US (Chessick et al., 2006; Millan, 2003; Millan et al., 2000c; Parmentier et al., 2013).

Regrettably, however, mirroring the downfall of neuropeptidergic agents in depression – and likewise reflecting a poorly-founded obsession with high selectivity – drug interacting with Neurokinin 1, Corticotrophin Releasing Factor 1 and Cholecytokinin-B receptors, despite encouraging preclinical data, were never developed and deployed as anxiolytic agents (Griebel and Holmes, 2013; Holsboer, 1999; Kehne and Cain, 2010; Millan 2003; Van Megen et al., 1996). It it is warranted to mention the utility of propranolol for controlling performance anxiety (Huffman and Stern, 2007), but there clearly remains much progress to be made in the management of, for example, post-traumatic stress disorder and severe phobias. Various forms of psychotherapy, alone and combined with pharmacotherapy, are important strategies for coping with these problems and for anxiety disorders in general (Section 8.6).

Finally, recent investigations have focused on non-benzodiazepine mechanisms for countering insomnia, including manipulations of melatonergic mechanisms involved in regulation of the sleep–wake circle (Cardinali et al., 2012). Ramelteon does not bind to GABA-A receptors but interacts with high affinity at melatonin MT1 and MT2 receptors in the suprachiasmatic nucleus (Owen, 2006). This mechanism is believed to underlie its sleep-promoting properties. It received FDA approval in 2005 for the long-term treatment of insomnia.

2.6. Agents for treatment of Attention-Deficit Hyperactivity Disorder (Figure 5 and Table 1)

The first attempt to pharmacologically control what we today call ADHD (Lange et al., 2010) was made by the American physician, Bradley. In the 1930s, he discovered by chance that some children suffering from neurological disorders treated with benzedrine (a racemic mixture of dl-amphetamine) showed clear improvements in their behaviour and scholastic achievements, as well as a decrease in hyperactivity (Bradley, 1937; Gross 1995). Moreover, he identified a group of children with features corresponding to ADHD and they also responded favourably to benzedrine (Gross, 1995). In addition, their emotional reactivity was moderated and their social behaviour improved (Strohl, 2011). However, these important observations that children with behavioural problems resembling ADHD respond positively to a central stimulant went largely unnoticed for almost 25 years (Strohl, 2011), probably due to the dominance of psychoanalysis up to the 1960s and since little was known about the biological bases of ADHD (Cyr and Brown, 1998).

In fact, only in 1955 was the first drug, methylphenidate, approved by the FDA for treatment of “hyperactivity”. Methylphenidate is a substituted phenethylamine which, like a number of CNS stimulants, was first synthesised in 1944 by the chemist Leandro Panizzon (Panizzon, 1944) at Ciba-Geigy and marketed as “Ritalin” (Leonard et al., 2004; Lange et al., 2010). Although it was quite widely prescribed to hyperactive children in the 1960s, it's broad use to control ADHD in children only emerged in the 1990s, by which time the diagnosis of ADHD had become more widely accepted (Cyr and Brown, 1998; Lange et al., 2010). Thus, from the 1970s on, the early focus on hyperactivity (“Hyperkinetic Reaction of Childhood”) gradually morphed into an emphasis on deficits in sustained attention and impulsivity as the key symptoms in ADHD (Barkley, 2006; Douglas, 1972; Findling, 2008; Gross, 1995; Lange et al., 2010). This ultimately led to the more recent conceptualisation of ADHD as defined in Diagnostic and Statistical Manual (DSM)-IV (Correll et al., 2011; Rapoport, 2013).

Benzedrine has not been available for some time owing to the high frequency of central and peripheral side-effects (Cooper et al., 2011; Lange et al., 2010), and methylphenidate is currently the first line of treatment for children diagnosed with ADHD (Felt et al., 2014). In addition, its therapeutic use now extends to adolescents and adults with ADHD (Davidson, 2008). However, other drugs with central "stimulant" properties have also been introduced for

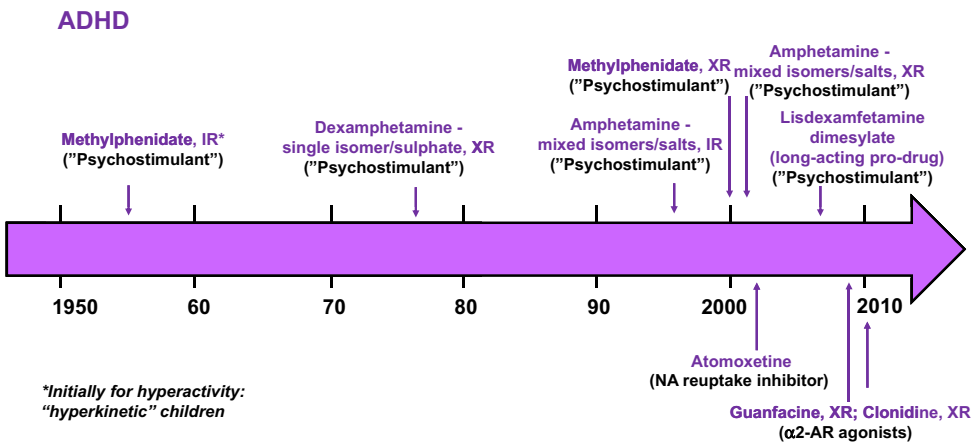

Figure 5 Schematic representation of the chronology for introduction of medication for the treatment of Attention Deficit Hyperactivity Disorder. The dates given are for approval by the FDA. The non-propriety, generic (WHO-approved) names of the drugs are indicated, not their commercial names which differ from region to region. Psychostimulants act *via* release and transporter mechanisms and atomexetine acts *via* NA transporters to elevate extracellular levels of NA (and DA). Clonidine and guanfacine directly stimulate post-synaptic α2-adrenergic receptors (AR). Not all drugs are shown, only those commented in the text and of particular significance in terms of their mechanistic and/or therapeutic profiles. Abbreviations: IR, Immediate Release and XR, extended Rrelease.

management of children and adults with ADHD-associated hyperactivity, impaired attention and impulsive behaviour (Cyr and Brown, 1998; Felt et al., 2014; Findling, 2008; Gross, 1995): interestingly, it is the latter two symptoms that display the most favourable response to treatment (Douglas, 1972). The major psychostimulant preparations used today (Figure 5) include rapid and extended release forms of: a mixture (mainly dextro) of amphetamine stereoisomers/salts; the dextro isomer of amphetamine alone; and the dextroamphetamine pro-drug with longer kinetics and lower abuse liability, lisdexamfetamine dimesylate (Castells et al, 2011; Dew and Kollins, 2010; Felt et al, 2014; Heal et al, 2013).

The mechanisms by which methylphenidate and psychostimulants exert their actions are multiple (Table 1). They principally involve presynaptic actions at transporters (membrane and vesicular), release mechanisms and trace amine associated receptors (Heal et al, 2013; Sulzer, 2005). This leads to elevated DA in ventral striatum (Volkow et al., 2012). They also enhance synaptic levels of DA and NA which should restore a hypothetical deficit in catecholaminergic transmission in the frontal cortex. This is important since an increase in frontocortical transmission will reinforce executive function, focused attention and top-down inhibition of impulsivity (Arnsten, et al., 1996; Barkley, 1997; Berridge and Arnsten 2013; Lange et al., 2010; Leonard et al., 2004). More recently, a selective inhibitor of NA reuptake was introduced to control ADHD, atomoxetine, approved by the FDA in 2002 (Felt et al., 2014; Garnock-Jones and Keating, 2009). Atomoxetine, has a more specific frontocortical mechanism of action than stimulants in that it does not interfere with synaptic release mechanisms nor vesicular monoamine uptake (Felt et al., 2014). A primary advantage over central stimulants (scheduled drugs) in the clinic is a lack of abuse potential (Felt et al., 2014; Garnock-Jones and Keating, 2009; Morton and Stockton, 2000). However, the full therapeutic effects of atomoxetine usually take 2–4 weeks to develop and its clinical efficacy seems to be somewhat lower than central stimulants, presumably since the dopaminergic component of activity is less pronounced (Felt et al., 2014; Garnock-Jones and Keating, 2009).

The above comments are consistent with observations that activation of (postsynaptic) α2A-AR receptors by the agonists, clonidine and guanfacine, is likewise effective active in ADHD. They were both authorised by the FDA in 2010, respectively alone and for adjunctive use with stimulants, in comparison to which they are less efficacious, most likely since they lack the D1 receptor component of activity recruited by stimulants (Arnsten, 2006; Bidwell et al, 2010; Connor et al., 2014; Felt et al., 2014; Sallee et al., 2013).

Finally, the importance of behavioural therapies should be mentioned and it should be noted that the historical terms "stimulants" or "psychostimulants" are hardly appropriate to describe the pharmacotherapy of children and adults with ADHD, and do not correspond to their core therapeutic benefits. This is one example underlying current interest in providing other systems of nomenclature for psychotropic agents (Zohar et al., 2014). Further, there is an important current debate about whether ADHD is, or is not, being excessively diagnosed and treated in children, in particular in the US (Arango, 2015; Rapoport, 2013).

2.7. How 60 years of neuropsychopharmacology is informing future R&D for improving the treatment of brain disorders

2.7.1. Steady progress, yet with a remaining need to enhance treatment efficacy

The above summary of the origins and further evolution of pharmacotherapy for psychiatric disorders covers a period of over six decades during which clinical progress was essentially incremental. There have been no radical paradigm-making (saltational) shifts leading to marked gains in efficacy after the first decade – though the important advances of both medication and *non*-pharmacotherapeutic strategies should not be neglected. Indeed, for responsive patients, increased choice

plus sure and steady progress in symptom relief with improved tolerance and safety is not a trivial achievement. However, there is now a consensus that further advances are imperative to enhance *effectiveness* both in refractory and in partially-responsive subjects – and ultimately to slow or prevent disease onset and progression (Carpenter and Koenig, 2008; Cuthbert and Insel, 2010, 2013; Kupfer et al., 2013; Sabbag et al., 2011).

For this to happen, although the foundations have been laid, much more must be learned about the causes and neurobiological bases of psychiatric disorders than in the past 60 years (Munos, 2009).

2.7.2. The importance of solid clinical feedback for novel mechanisms: on the issue of its absence

One fundamental pillar of the learning process of neuropsychopharmacology is the generation of reliable and confirmed data on efficacy from patients in the course of clinical trials of novel therapeutic concepts and mechanisms of action. However, in many cases where medication has failed (Section 8.4), it is difficult to be certain that the drug/concept was given a real chance, not least in view of nagging questions concerning the choice of patient population, maximal tolerated dose, and whether target engagement was sufficient for efficacy to be expressed.

One reason for the latter uncertainty has been the lack of specific biomarkers such as a Positron Emission Tomography ligands for defined classes of receptor/transporter. While radiolabelled ligands are available for, say, D2, 5-HT1A and Neurokinin 1 receptors as well as monoamine transporters, despite considerable efforts, no equivalent agent has ever been generated for 5-HT2C, metabotropic glutamate 2 or Corticotrophin Releasing Factor 1 receptors, complicating development of agents targeting these sites (Catafau and Bullich, 2013; Ratti et al., 2011). Efforts to search "upfront" for translational biomarkers of target occupation (and medication effectiveness) early in the R&D process are considered in Section 8 (Chandler, 2013; Doehrmann et al., 2013; Harmer et al., 2011; Scarr et al., in press).

However, perhaps the most frustrating examples of absent feedback from patients are for targets/mechanisms of action where preclinical observations are highly compelling yet clinical data have never been, for a variety of commercial, strategic and/or practical reasons, generated. For example, despite the fact that every single clinically-useful antipsychotic binds with equal affinity at D2 and D3 receptors, and a substantial data base supporting use of the latter for promoting cognition and countering drug-seeking behaviour, no data from patients are available with selective D3 antagonists in schizophrenia (Heidbreder and Newman, 2010; Millan et al., 2007; Mugnaini et al., 2012; Watson et al., 2012). There are innumerable other examples, such as various classes of neuropeptidergic receptor, kinase antagonist inhibitor and so forth.

Thus, an awful number of holes still remain to be plugged – and pieces of the jigsaw to be fitted – before we will have a completer picture of the neuropsychopharmacology of psychiatric disorders. This remains a task for the future, but one approach to help resolve this situation is Experimental Medicine using discontinued drugs clinically proven to be safe and possessing well-defined and novel, as yet untested, mechanisms of action (Section 6.3).

2.7.3. Key messages concerning pharmacotherapeutic agents and drug development

As regards pharmacotherapy and drug development, there are a number of significant messages worth retaining for future reference, several of which are discussed in other Sections of this article.

First, not all drugs have their origins in ostensibly "rational" target-based drug discovery, which has been heavily subsidised since the 1990s, mainly driven by technological advances like High-Throughput-Screening (HTS). In fact, many drugs emerged from more standard, "low" throughput paradigms and from the evaluation of compounds in integrated systems (Rask-Andersen et al., 2011; Swinney and Anthony, 2011). Intriguingly, the latter approach of phenotypic screening is enjoying something of a renaissance, in particular using new cellular models (Section 6.2)

Second, at the other (patient) end of R&D, major therapeutic advances were not necessarily based on cogent psychopharmacological, mechanistic and clinical reasoning – in some cases since the mechanism of action of the drug in question was unknown. Rather, in particular during the emergence of medication for psychiatric disorders in the 1950s, perspicacity and *serendipity* were key elements. This alludes to above-mentioned progress (Section 2) made by astute and imaginative clinicians supported by perceptive pharmacologists and creative chemists. Indeed, serendipity is likely to remain psychiatry's friend and it is critical to foster the experimental spirit and knowledge that can discover both the true vocation of novel agents, as well as new indications for any specific treatment whatever its original use (Sections 6.3 and 8.4).

Third, in most cases, though we are not entirely in the dark, we do not have a precise idea of exactly how drugs work, mirroring uncertainty regarding the pathophysiological causes of psychiatric disorders. Again, better knowledge would be important for future progress (Section 4).

Fourth, in line with the previous points, all drugs are a work in progress. A sustained effort in experimental and clinical studies throughout their lifetimes is desirable to better understand their pharmacologic and pharmacokinetic properties, clinical actions (beneficial and deleterious) and therapeutic utility. It is impossible to pre-programme and anticipate everything from the word "Go"!

Fifth, partly as a function of such incremental and updated knowledge, drugs may conquer new territories in terms of clinical application (repurposing) (Section 6.3). Bupropion for smoking cessation and SSRIs for anxiety disorders are examples, as well as SGAs for bipolar disorder. The recent difficulties of getting new chemical entities into patients are encouraging an expansion of this strategy (Section 6.3).

Sixth, no drug is selective, but some are less selective than others. This is not necessarily a bad thing. On the contrary. However, as exemplified by the pros and cons of clozapine and TCAs, it would be advisable to choose by dialling in and out beneficial and deleterious properties, respectively. This is the core concept underpinning multi-target treatments for complex disorders (Section 7.1).

Seventh, for a specific psychiatric disorder, or domain of dysfunction, multiple mechanisms of action are usually effective for symptom relief. This is consistent with biological

redundancy in the control of core functions like cognition and mood, and also with the multi-factorial nature of psychiatric disorders. This point suggests that we can intervene at several distinct nodes in anomalous networks, though whether there is convergence onto one common substrate is not yet clear (Fornito and Bullmore, 2015; Millan, 2006; Nussinov et al., 2011). In any event, such observations encourage the future pursuit of *several* different mechanisms of action – alone and in tandem – for treatment of psychiatric disorders and their attendant symptoms (Millan, 2014a). Contrariwise, for one specific mechanism of action, diverse beneficial effects may be expressed across a number of contrasting diagnoses or domains of impairment. Again, this encourages an open and flexible approach to the prospective clinical evaluation of novel concepts and mechanisms of action, as well as the need to be alert as regards unanticipated effects – unwanted as well as desired (Section 8.4).

Eighth, there is currently much scepticism concerning the relevance of *in vivo* animal models and behavioural tests of psychotropic agents to the actions of medication in humans. However, it stretches credulity to imagine that moving even farther away from the human brain to, say, zebrafish larvae, would (despite certain useful applications, Section 6.2) be more instructive – while similar issues of data reliability would be faced. In fact, all currently-employed antipsychotic, antidepressant and other classes of agent *are* active in specific behavioural paradigms in rodents. Further, some models and readouts like the conflict test for anxiety and the forced-swim test for antidepressants, despite obvious limitations, pick up diverse classes of compound. Hence, they can hardly be considered as superfluous. The challenge remains of *improving* these models in particular in terms of responsiveness to novel mechanisms of action. This implies avoiding both false positives (only seen in the clinic) and false negatives (which we will never know about). Back-translation of active agents to animal procedures (mirroring the early days of the TCAs, Section 2.3.1) is of importance here (Section 8.4). The history of neuropsychopharmacology suggests that it would be very unwise to abandon rodent-behavioural models and to jump straight into humans, in particular in view of current progress in their improvement within a translational framework (Sections 5 and 8).

Ninth, pharmacotherapy is critical, but it is unlikely ever to be enough alone for the control of all symptoms in all patients. In many cases, it may best be used in conjunction with psychotherapeutic, simulation and rehabilitative approaches. Hence the importance of studying and associating complementary therapeutic strategies to protect and help patients as a function of their symptoms, pathophysiologies, needs and convictions (Section 8.6).

Finally, while 60 years may appear a long time, progress in our knowledge of the brain has been phenomenal, in particular at the molecular level and this period is rather modest in relation to a normal human life-span. Even if we were to require another 60 years to more comprehensively and profoundly understand the brain, to work out why things go wrong, and to learn how to put them right, this would correspond to no more that the (at this time) recognised maximal life-span (122 candles for Jean Calment). And 60 years is less than one thousandth of the estimated time for the presence of (anatomically-modern) *Homo sapiens sapiens* on this planet.

2.8. Sequencing the human genome and its dubious impact on drug discovery for psychiatric disorders

From a historical perspective, a few remarks should be made on how the sequencing the human genome influenced drug discovery for CNS disorders. Merely the announcement that the genome was going to be sequenced led to the naive hope of some (aggravated by hype from others) that a vast panoply of novel genes-proteins-mechanisms were going to be revealed to explain the function and dysfunction of the human brain, and *ipso facto* to provide an inexhaustible palette of novel targets for ("personal") medication. The genomic balloon began to deflate with the realisation that, regulatory zones of DNA/RNA notwithstanding, the total number of gene-coding proteins was nothing exceptional compared to, say, a cabbage, and later, that the number of hitherto-unexploited targets was fairly modest – with only some relevant to CNS disorders (Drews 2006; Graur et al., 2013; Pertea and Salzberg, 2010; Rask-Andersen et al., 2011). Unfortunately, this did not prevent the at least temporary neglect of other "genome-free" R&D programmes and the diversion of enormous resources to the identification of the genetic risk factors for/causes of disorders – the latest chapter being the current vogue for Genome-Wide Association Studies (GWAS) and cut-price, individual genome-sequencing. Another problem at that time was the (outrageous) locking up of potential new targets by dissuasive patents: chromosomal locus, gene, protein, method of screening, therapeutic use etc. This ironically *reduced* rather than increased target availability. This was often coupled to a simplistic one gene-one disease-one drug mindset for (in fact idiopathic, polygenic, multifactorial) CNS disorders, and the – with hindsight – naive belief that nominally "Rational" drug discovery driven by HTS and combinatorial chemistry (the "magic of high numbers") would simplify and accelerate the discovery and development of novel (highly selective) and more efficacious agents (Drews, 2006; Millan, 2006, 2014a; Pertea and Salzberg, 2010; Rask-Andersen et al., 2011). It didn't.

To cut a long story short, sequencing the human genome did not provide the hoped-for quick fix. On the other hand, it is now providing an indispensable source of knowledge that is being progressively exploited to better understand the function and dysfunction of the brain, to identify reliable biomarkers of psychiatric disorders, and to help identify and validate novel treatments for their relief. *This* story has just begun.

3. Clinical characteristics and causes of psychiatric disorders (Table 2)

3.1. Normal and healthy states: defining the boundary to psychiatric disorders

By analogy to other diseases, a psychiatric disorder inherently implies a difference between normal and abnormal. The events related in Section 2 unfolded largely within a diagnostic framework dominated by the DSM and International Classification of Disorders (ICD) which still play important roles in defining the boundary between well and unwell (Section 3.2). This boundary is used as a criterion for therapy, with the evidence basis of the treatment in question defined by rigorous clinical trials

Table 2 Overview of recent changes in thinking and performance of R&D for psychiatric disorders as concerns their clinical characterisation and causes.

Area of R and D	*Recent and future developments*
Diagnosis and clinical characteristics of psychiatric disorders	Better documentation and quantification of the precise cost and burden of psychiatric disorders. Progressive erasure of artificial barriers between Psychiatry and Neurology, and between Psychiatry and Psychology (disease characteristics, causes, pathophysiology, study, etc). More attention to differentiation of psychiatric disorders from "normality". Integration of dimensional (domains of dysfunction) with categorical (class of disorder) criteria in the classification of psychiatric disorders. Domains of dysfunction and pathophysiological substrates that cut across traditional nosological borders, over and above co-morbidity. Better linking of symptoms/dysfunction to pathophysiological substrates. Shift in focus from neurocognition to key importance of impaired social cognition/processing for psychiatric disorders: more closely linked to real-world dysfunction. Idiopathic psychiatric disorders genetically complex: identification of putative genetic markers (clusters) for diagnosis and stratification challenging: needs multivariate methods of validation in large samples, then confirmatory studies. Need for multi-modal biomarkers of psychiatric disorders, domains of dysfunction and underlying pathology (genetic, EEG, imaging, neurocognitive readouts): both for diagnosed patients and for high-risk subjects.
Risk factors, causes and pathophysiological substrates of psychiatric disorders	Psychiatric disorders are multifactorial: gene-gene and gene-environment interactions critical, especially during development. Innumerable minor effect genes: certain *de novo* high impact CNVs and rare, deleterious mutations. Somatic and mitochondrial mutations. Epigenetic (de)regulation can scramble genetic links to psychiatric disorders. It partially transduces impact of environmental risk factors. Source of novel biomarkers and drug targets. Additional mechanisms underlying impact of environmental risk factors, including their interaction with genetic risk factors, need more intensive study. Both molecular (reductionist) *and* circuit (systems) analyses of causes and pathophysiological substrates of psychiatric disorders essential. Not just perturbed neurotransmission: many processes disrupted like synaptic plasticity, mitochondrial integrity, neuronal migration, and neurogenesis. Not just neuronal dysfunction: likewise abnormalities of glia (astrocytes, oligodendrocytes, microglia) incriminated in psychiatric disorders. Roles for neuroendrocine (other organs) and auto-immune mechanisms. Exotic factors; intestinal microbiome, viral/bacterial infection and parasites. May converge on central mechanisms like immune-inflammatory processes. Certain external and endogenous mechanisms protect from psychiatric disorders: e.g. green environment and epigenetic programming, respectively.

The table summarizes the points discussed in more detail in the text. CNV, copy number variant and EEG, electroencephalography.

(Section 8). The issue remains of how to objectively specify the boundary not only between disorders but also between health and disease which, in contrast an acute bacterial infection, is more ambiguous to define. Indeed, the criticism has been made that psychiatric disorders lie on a spectrum of experience continuous with normality since " healthy" subjects may display transient, mild and isolated symptoms of anxiety, depressed mood and even psychosis (Copeland et al., 2011; Ford et al., 2014; Kawa and Giordano, 2012; Kupfer et al., 2013; Stein, 2013; Varga, 2011). This remains under discussion, but is not

inconsistent with the enormous overlap for most biomarkers in studies of ill *vs* well populations, and gradients of cumulative genetic load across a broad range of phenotypes from healthy to umambiguously ill (Cannon et al., 2015 Fusar-Poli et al., 2013; Doherty and Owen, 2014; Scarr et al., in press).

In fact, several other chronic diseases likewise do not suggest a neat dichotomy between normal and abnormal. This is illustrated by hypertension and measures of blood pressure, as well as by similarly controversial interpretation of deviations in circulating levels of cholesterol, glucose and prostate-specific antigen (Robinson et al., 2014; Rosa et al., 2014). Moreover, for psychiatric disorders, the definition of "healthy" is especially complex and ambivalent since notions of normative behaviour and well-being may vary from person to person and population to population as a function of context, upbringing, religion, culture and age etc (Cloninger, 2006; Harris and Deary, 2011; Khoury et al., 2014).

Nonetheless, appropriately demarcating psychiatric disorders from a "normal" or typical phenotype and range of variation is important in order to avoid: underestimation *and/or* over-inflation of prevalence rates; under-treatment *and/or* excessive medicalisation; risky behaviour in the false belief that one is not at risk *and/or* false attribution of a psychiatric disorder (Butlen-Ducuing et al., 2012; Corrêa Coutinho et al., 2010; Khoury et al., 2014; Kawa and Giordano, 2012; Nutt, 2012; Stein, 2013). For example, there has been much discussion regarding the growing prevalence and treatment of ADHD in the US over the past decades (Arango, 2015; Correll et al., 2011; Rapoport, 2013). Conversely, it is critical not to ignore early warning signs of the imminent or future emergence of a psychiatric disorder (Cannon et al., 2015; Fusar-Poli et al., 2013; Kupfer et al., 2013; Stein, 2013). Notwithstanding developmental and age-related changes in mood, behaviour and cognition, in the course of *longitudinal* studies, marked and unexpected shifts in mood or cognition are a sign of something wrong – especially when associated with distress and help-seeking (Fusar-Poli et al., 2013; Fjell et al., 2014; Harris and Deary, 2011).

In considering the question of what is abnormal prior to instigating preventive therapy, it is again interesting to consider the parallel with statins used for precluding onset of cardiovascular disorders based on circulating levels of cholesterol (Rosa et al., 2014). What we currently lack in psychiatry are: reliable biomarkers of risk even where appearances are "normal"; very safe drugs for treatment of vulnerable people; and large-scale studies demonstrating their benefit in an at-risk population. Nonetheless, as discussed in Section 7.3, we are moving towards that goal, at least as regards young people at clinically-high risk of transition to schizophrenia (Fusar-Poli et al., 2013).

The distinction between healthy and ill can, then, be challenging, though recent studies emphasise that the vast majority of treatment is indeed devoted to patients with disorders of mental health (Al-Hamzawi et al., 2015; Nutt, 2012). The related point of when "mild" turns into serious also warrants brief mention with respect to clinical trials and real world treatment, since the efficacy of medication in severe states may not always be reproduced for milder forms (Butlen-Ducuing et al., 2012; Cameron et al., 2014; Cuthbert and Insel, 2010).

3.2. Categorising and discriminating between psychiatric disorders, the advent of DSM-5

Apart from the pressing question of differentiating psychiatric disorders from the "normality" to which treatment should regress, a further critical issue is the discrimination between specific psychiatric disorders themselves, and their overall classification. This is a far from simple process, which commenced around the time of Kraepelin and Bleuler, and is still on-going as embodied by successive World Health Organisation coordinated editions of the ICD (mainly for general practitioners and educational use) and of the American Psychiatry Association-sponsored DSM (mainly for psychiatric specialists and clinical research) (Butlen-Ducuing et al., 2012; Casey et al., 2013; Hyman, 2007, 2010; Kawa and Giordano, 2012; Kupfer et al., 2013). Though output is widely respected and recognised by companies, regulators, clinicians and others involved in R&D, classification is still a source of debate which has been re-ignited with the recent appearance of DSM-5. Amongst other new features aiding clinical practise, DSM-5 is designed to improve coherence with the ICD and to better reflect the needs of patients (Butlen-Ducuing et al., 2012; Cuthbert and Insel, 2013; Kawa and Giordano, 2012; Khoury et al., 2014; Kupfer et al., 2013; Mellsop et al., 2007; Phillips et al., 2012; Regier et al., 2013).

In fact, some might provocatively debate whether there is an absolute need for a diagnostic system by categories of disorder, since a standardised diagnosis can become disconnected from underlying mechanisms in grouping together either too many (or too few) individual cases. For example, the over-extension of the notion of schizophrenia in North America during the 1950s and 1960s eventually compromised its significance, and it is possible that an analogous problem with bipolar diagnosis in childhood is causing similar problems today. Nonetheless, this does not invalidate the approach, rather incites greater care and thought into the discrimination of diagnostic groups, as attempted by DSM-5 (Kupfer et al., 2013). Moreover, at least initially, a diagnosis is less of a fact, rather more of a hypothesis awaiting proof of concept before final confirmation. In addition, categorising disorders (and treatments) as best we can is important for accessing the scale of psychiatric disorders in society, for evaluating the utility of treatments for reimbursement and for communicating with patients.

Concomitantly with this ongoing discussion as to how best to clinically classify psychiatric disorders, a parallel, equally-important and more research-driven process is underway to better understand their neurobiological substrates. It is to be hoped – and cautiously anticipated – that these paths will ultimately converge (see following Section).

3.3. Comorbidity amongst psychiatric disorders: trans-nosological domains of dysfunction

Clinical practise and the literature are dominated by the diagnostic categories of schizophrenia, bipolar disorder and depression etc (Table 1), and they are likely to remain omnipresent and indispensable for the foreseeable future. However, their precise significance in terms of core features and neurobiological underpinnings remain under clarification, and heterogeneity is increasingly recognised in terms of risk

factors, pathophysiology, symptoms, outcome and – as a consequence – treatment. Indeed, the very fact that diagnostic categories are defined by symptoms poorly linked to underlying pathophysiology suggests that they are likely to be heterogeneous.

The occurrence of extensive co-morbidity amongst psychiatric disorders, and between psychiatric disorders and physical complaints, is now widely recognised – and associated with greater disease burden (Brown, 1996; Buist-Bouwman et al., 2005). However, overlap appears to be more fundamental than the mere co-existence of two distinct disorders. Thus, the traditional notion of *co-morbidity* is yielding to a more complex view of communalities between nominally-independent yet neurobiologically-related disorders including, for example: genetic risk factors, epigenetic misprogramming, stress axis deregulation, neuroinflammation, disruption of synaptic plasticity, and abnormal glutamatergic transmission. In addition, deficits in core functional domains like neurocognition, social processing, reward and affect likewise cut across traditional boundaries. The improved characterisation of deficits and pathophysiological mechanisms specific to discrete disorders (or sub-types of disorder) as compared to those shared with others should facilitate the identification of more discriminant biomarkers of greater reliability (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Cuthbert and Insel, 2010, 2013; Doherty and Owen, 2014; Grabrucker et al., 2011; Harrison, 2014; Hyman, 2007; Kupfer et al., 2013; McGowan and Szyf, 2010; Millan et al., 2012; Millan, 2013; Muglia, 2011; Scarr et al., in press).

It has been pointed out that a trans-nosological clinical trial of, say, deficient working memory would hardly be less challenging than a psychiatric disorder-specific clinical study (Butlen-Ducuing et al., 2012). In addition, the risk of patients needing a cocktail of specific treatments with one per pathophysiological mechanism/symptom (impaired working memory, social processing deficits or poor motivation etc) should be borne in mind. Further, it is important not to put the cart before the horses in forcing clinical syndromes to match pathophysiological substrates: at the end of the day, it is symptoms that patients suffer from and that they want to see improved, not putative biomarkers.

Nonetheless, these points should not detract from this important goal of improved characterisation and differentiation of psychiatric disorders, including the more refined alignment of populations targeted for clinical trials/treatment with pathological mechanisms underlying dysfunction. One major initiative in this regard is the "RDoc" programme of the National Institute of Mental Health (Casey et al., 2013; Cuthbert, 2014; Cuthbert and Insel, 2010, 2013; Phillips et al., 2012; Simmons and Quinn 2014). The RDoc programme does *not* stand in opposition to current clinical classifications since, as implied, it is a research-driven enterprise which aims to better classify trans-diagnostic dimensions of disease within a biological framework. Its outcome should eventually merge with new diagnostic schemes to mutual benefit. It has a strong translational flavour (validated measures adaptable for human use), emphasises the need for improved animal models (Section 5), puts behavioural, neurobiological and genetic findings on equal footing, and embraces the notion of endophenotypes or intermediate phenotypes. Intermediate refers to the fact that a specific anomaly (like impaired executive function) lies between a genetic aberration and a psychiatric disorder and hence should be more closely linked to the causal gene (Goldstein and Klein, 2014; Hasler et al., 2006a, 2006b). RDoc attempts – in a trans-nosological and dimensional manner – to define the pathophysiological substrates of psychiatric disorders for general domains like neurocognition, affect, social processing, arousal and reward (Cuthbert and Insel, 2013; Kas et al., 2007; Marcou et al., 2009; Robbins et al., 2012). This should eventually aid both the discovery and validation of novel treatments, and promote the (pre and post diagnosis) detection of more reliable biomarkers of disease/pathophysiological states.

3.4. An ongoing process of refinement and convergence

To summarise, it is important to clearly differentiate psychiatric disorders from "normality" and to improve their clinical characterisation. Classification of psychiatric disorders remains a "work in progress" which is increasingly being informed by neuroscience and occurring in a transnosological context as regards underlying pathophysiological – and counter-regulatory – mechanisms. The more rigorous characterisation of psychiatric disorders, increased awareness of their similarities and differences, and their improved integration with neurobiology should ultimately permit 1), the development of more specific biomarkers and 2), the identification of more effective and focused treatments for specific populations (Cuthbert, 2014; Cuthbert and Insel 2013; Kawa and Giordano, 2012). Though the vision of pathology-based "precision medicine" for psychiatric disorders still remains distant, progress has now commenced towards this ultimate goal (Section 8.5).

4. Pathophysiological substrates of psychiatric disorders: multiple anomalies from molecules to cerebral circuits (Table 2)

4.1. Insights from neurological and somatic disorders

By analogy to all other organs, disruption of the brain is associated with specific pathologies, as exemplified by Stroke, Parkinson's disease and Alzheimer's disease with their attendant structural damage. As indicated in Table 1, the artificial divide between neurological and psychiatric disorders is being progressively effaced with the recognition that, quite apart from co-morbidity and common risk factors, they share common domains of dysfunction in mood and cognition (Cunningham et al., 2006; Hirao et al., 2014; Millan et al., 2012; Millan et al., in press; Norton et al., 2014; Sierksma et al., 2010). Likewise contributing to the erosion of this artificial divide is the realisation that psychiatric disorders are characterised by *structural* changes in the brain – such as altered size of the hippocampus – involving disruption of both grey and white matter, neurones and glial cells (Arnone et al., 2013; Bartzokis, 2012; Brent et al., 2013; Buckholtz and Meyer-Lindenberg, 2012; Czeh and Di Benedetto, 2012; Kempton and McGuire, in press; Smiałowska et al., 2013; Watkins et al., 2014; Zhang et al., 2015). Further, certain molecular facets of age-related disorders, like reelin dysfunction, epigenetic misprogramming and mitochondrial bioenergetic defects are also implicated in

psychiatric disorders (Clay et al., 2011; Folsom and Fatemi, 2013; Klengel et al., 2014; Knuesel, 2010; Krstic et al., 2013; Manji et al., 2012; Millan 2013, 2014b; Morales et al., 2014; Szyf, 2015; Szyf and Bick, 2013; Wallace, 2013; Zhang and Meaney, 2010). Both Alzheimer's disease and multiple sclerosis are characterised by neuroinflammation, and in the latter case, by focal brain lesions and demyelination (Ellwardt and Zipp, 2014; Wyss-Coray and Rogers, 2012). Similarly, inflammatory damage to oligodendroytes, aberrant patterns of myelinisation and white matter loss have been implicated in the genesis of schizophrenia (Bartzokis, 2012; Leboyer et al., 2013; Perron et al., 2012; Najjar and Pearlman, 2015; Ren et al., 2013; Von Hohenberg et al., 2014). A rapprochement between neurological and psychiatric domains should be fostered and intensified to mutual benefit since both can learn much from each other.

Novel insights into the causes of psychiatric disorders are also being gained by studies of other organs and *non*-CNS diseases such as diabetes and obesity (Karsenty, and Ferron, 2012; Labarthe et al., 2014). These risk factors for depression may be functionally linked to, for example, aberrant signalling by the gut-released and CNS-penetrant hormone, ghrelin, which centrally controls mood and cognition as well as appetite (Carlini et al., 2012; Chuang and Zigman, 2010; Labarthe et al., 2014; Millan, 2014a; Shelton and Miller 2010). Another example is provided by oncology where changes in mechanisms of neuro-immune-endocrine crosstalk, cellular signalling and circadian control have been related to an inverse correlation between schizophrenia and Down syndrome on the one hand, and certain cancers on the other (Tabares-Seisdedos and Rubenstein 2013).

4.2. Linking the genetics of psychiatric disorders to causal mechanisms and targets

A widely-used approach to examine the aetiology of psychiatric disorders, and to search for potential biomarkers, is psychiatric genetics (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; GENDEP Investigators, 2013; Harrison, 2015; Karayiorgou et al., 2012; Levinson et al., 2014; Muglia 2011). In view of its intensive study, schizophrenia serves to illustrate recent developments of the field. In contrast to rare neurodevelopmental forms of Autism-Spectrum Disorder (ASD)-related syndromes like Fragile X or Rett (Millan 2013), monogenic forms of schizophrenia are unknown (Muglia, 2011; Winchester et al., 2014). Further, despite high heritability, candidate gene (single nucleotide polymorphism) association studies have not revealed any robust, common and specific genetic signals underlying schizophrenia – nor other psychiatric disorders. Rather, numerous, rare, inherited or *de novo* risk loci (single genes to CNVs) appear to be involved, consistent with the notion that multiple nodes of cellular circuits are disrupted in psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Fromer et al., 2014; Levinson et al., 2014; Doherty and Owen, 2014; Purcell et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In addition, candidate gene studies have often failed to replicate published studies suggesting that underlying genetic architecture is complex and that interactions amongst genes in heterogeneous, small populations may influence study outcome (Franck and Fossella, 2011; Greene et al., 2009; Muglia, 2011). Supporting comments in Section 3.4, several genetic risk loci ignore nosological categories and are shared amongst schizophrenia, bipolar disorder and ASD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Doherty and Owen, 2014; Muglia, 2011).

Massive, unbiased GWAS can confirm (or refute) candidate gene identification and reveal hitherto-unsuspected risk genes: they also permit pathway analyses to interlink genes into circuits of interacting proteins. The biggest GWAS study to date of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) recently confirmed that no specific common variant has any major impact, and that this polygenic disorder involves thousands of loci of modest impact accounting for about half of genetic variance (Harrison, 2015; Purcell et al., 2014; Ripke et al., 2013). Further, it should not be forgotten that the significance of any genetic variant requires direct functional analysis (Dolgin, 2014; Muglia, 2011). Nonetheless, some positive aspects should be highlighted from this GWAS study of schizophrenia since D2 receptors (not exactly a novel target) were only one of 108 loci (including 83 novel ones) identified (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In this and other large-scale studies, the frequent appearance of genes related to synaptic plasticity, glutamatergic transmission, immune-inflammatory processes and ion channels is interesting; products of several genes such as "CACNA1C" (encoding a Ca^{2+} channel subunit), are eminently druggable (Fromer et al., 2014; Keller and Muller, 2006; Harrison, 2015; Muglia, 2011; Purcell et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Furthermore, several classes of CNV have been found to be highly penetrant in small populations. For example, 22q11.2 is associated with velocardiofacial (Di George) syndrome, a rare disorder with a very high risk of schizophrenia (Kirov et al., 2013; Millan, 2013; Sigurdsson et al., 2010). While covering many protein-coding and other genes, CNVs can be studied in both cellular and murine models, the functions of individual genes clarified and further analysis at the mRNA and protein level undertaken in schizophrenic tissue. This can be followed by genetic profiling of volunteers in relation to say cognitive performance and fMRI-defined circuits in patients (Buckholtz and Meyer-Lindenberg, 2012; Kempton and McGuire, 2014; Nomura and Takumi, 2012). Such observations provide raw material for back-translation into animal models and further characterisation of potentially-novel treatment targets (Meyer-Lindenberg, 2010). Further, at least for schizophrenia, bipolar disorder and ASD, it would be rewarding to search for rare, recurrent, highly penetrative, causal deleterious mutations by focusing on defined and small regions of the genome: not only in CNVs, but also in regions like those embraced by the 108 loci associated with risk for schizophrenia (Karayiorgou et al., 2012). More attention to somatic mutations during development (Insel, 2014) and non-Mendelian mitochondrial genetics might also be instructive (Wallace, 2013).

Overall, psychiatric genetics still has a major role to play as a point of departure for more refined analysis of potentially relevant proteins and novel therapeutic strategies. Further, it is important to consider genetic pathways rather than single genes, to examine the interaction of genetic with environmental factors, and to see how they collectively impinge upon neural circuits interrupted in psychiatric disorders (Brown and Derkits, 2010; Buckholtz and Meyer-Lindenberg, 2012; Caspi et al., 2003; Muglia 2011; Wang et al., 2010; Winchester et al., 2014).

Psychiatric genetics should ultimately help us towards a more informed view of the cellular and cerebral circuits disrupted in psychiatric disorders.

4.3. Scrambling the genetic message: epigenetic re-programming

It's a long way from the gene to the protein, and many mechanisms can intervene to markedly modify protein dosage, structure and function: altered gene transcription; covalent, post-translational protein modifications like phosphorylation; formation of higher-order protein oligomers; and association with other proteins as in heterodimers. Such processes may be anomalous in psychiatric disorders. However, of particular importance are potentially-heritable (meiosis and mitosis) epigenetic changes that, at the level of DNA promoter methylation, the histone code and miRNA control of mRNA translation, modify the genetic message and protein availability (Kofink et al., 2013; Klengel et al., 2014; Mehler, 2008; Millan, 2013; Szyf, 2015). There is compelling evidence that environmental impacts throughout life, and in particular during development and maturation, strongly impact epigenetic mechanisms. While some changes may be adaptive (Section 4.7), most are likely implicated in the pathophysiology of psychiatric and neurological disorders (Brown and Derkits, 2010; Gavin, and Floreani, 2014; Kofink et al., 2013; Millan 2013, 2014b; Szyf and Bick, 2013; Szyf, 2015). This adds a new and therapeutically-relevant domain of complexity to our modern understanding of the long and winding road from genetics to psychiatric disorders.

4.4. The view from above (and below): the crucial importance of networks

It is now clear that the impact of genetic, epigenetic and other anomalies, even if triggered by a single molecular event, must be understood and analysed at the level of dysfunctional networks, both *in* and *of* neurones. This includes, for example, epistatic interactions amongst genes, signalling cascades, and circuits of neurones interlinking the hippocampus and cortex. While not ignoring the functions of discrete proteins, cells or regions, it is their aberrant interplay and the disruption of networks that needs to be re-equilibrated by therapy (Broyd et al., 2009; Buckholtz and Meyer-Lindenberg, 2012; Fornito and Bullmore, 2014; Menon, 2011; Millan et al., 2012; Penrod et al., 2011; Silverman and Loscalzo, 2012; Wang et al., 2010). The study of networks is often subsumed under the term "Systems" biology and now profits from extensive computerised modelling and the application of Graph Theory. This refers to mathematical models of complex networks, their organisation and operation in health, their dysfunction in disorders like schizophrenia and depression, and strategies for their restitution (Bolding et al., 2012; Fornito and Bullmore, in press; Kotaleski and Blackwell, 2010; Mei et al., 2012; Millan 2006; Phillips et al., 2012; Sams-Dodd, 2013; Van den Heuvel and Fornito, 2014).

4.5. Multiple anomalies across a diversity of cell types: identifying the primary trigger

It should be added that aberrant events in neurones are played out in interaction with non-neuronal cells like astrocytes, oligodendrocytes and microglia which fulfil a more prominent place in the search for the origins of psychiatric disorders than some years ago. Glial dysfunction in depression, aberrant developmental myelination in schizophrenia and microglial-driven inflammation in autism are examples that spring to mind (Bartzokis, 2012; Basnasr et al., 2010; Bernstein et al., 2015; Di Benedetto et al., 2013; Perron et al., 2012; Smiałowska et al., 2013).

The notion of disrupted neurotransmission as a causal factor for psychiatric disorders, such as excess mesolimbic DA in schizophrenia, or a deficit in 5-HT in depression, is well established (Artigas, 2013; Meltzer, 2013; Millan, 2003, 2006). Upstream, downstream and in parallel with anomalies in neurotransmission, there is a rich panel of other cellular mechanisms known (or suspected) to be disrupted in CNS disorders and potentially available for therapeutic exploitation. Examples include neurogenesis and mitochondrial energy production (Clay et al., 2011; Duman and Voleti, 2012; Gorman et al., 2012; Manji et al., 2012; Wallace, 2013). However, there is still very much a chicken and egg situation in which, both in time (during life and prior to diagnosis) and space (cellular networks), we need to better tease out which are the initial and primary anomalies from which others cascade. For example, hyperactivity and hypersensitivity of subcortical dopaminergic projections in schizophrenia must exist at the interface between both prior disruption (possibly of frontocortical glutamatergic pathways) and downstream events in postsynaptic neurones (Millan et al., 2012; Poels et al., 2014).

4.6. Causal factors extrinsic to the brain

A brief word on exotic, brain non-autonomous mechanisms should be made. Recently, a possible role of anti-neuronal antibodies in triggering psychiatric and neurological syndromes was evoked, for example by compromising activity at central N-Methyl-D-Aspartate (NMDA) receptors (Martinez-Martinez et al., 2013; Van Coevorden-Hameete et al., 2014). A particularly intriguing idea is that mental health can be negatively impacted by parasites, as well as bacterial and viral triggers of CNS disorders (Eppig et al., 2010; Leboyer et al., 2013). Viruses penetrate into the brain *via*, for example, immune cells and long-range axonal transport. Once inside, they can provoke numerous adverse effects including the fabrication and hijacking of G-protein coupled receptors (GPCRs) and the reactivation of retroviruses in multiple sclerosis and, more speculatively, schizophrenia (Leboyer et al., 2013; Perron et al., 2012; Salinas et al., 2010a, 2010b; Sodhi et al., 2004). Further, one – unanticipated – factor that may contribute to psychiatric disorders has transpired to be the microbial flora of the gut. Though specific links to discrete diseases remain to clarify, perhaps the most compelling body of evidence to date suggests a link to idiopathic ASD (Foster and McVey Neufeld, 2013, Mulle et al., 2013; Nemani et al., 2015).

4.7. Mechanisms opposing the genesis of psychiatric disorders

Finally, it was mentioned above that not all epigenetic changes during life are maladaptive, for example those improving the

ability to cope with stress (Szyf and Bick, 2013; Millan, 2014b). Indeed, for every circumstance in which one identifies a change in a parameter that increases the risk of a psychiatric disorder, one can turn the argument on its head, be it an allele or a level of transmitter secretion, in arguing that the inverse change is in fact a *protective* mechanism. While GWAS and hypothesis-driven studies almost invariably aim to pinpoint rare variants and *de novo* anomalies *causal* to disorders, there very likely exist others (inherited and subject to positive rather than purifying selection) that are *protective*. This was recently demonstrated for certain CNVs (Grozeva et al., 2013; Doherty and Owen, 2014; Rees et al., 2014). More attention, in particular in the light of preventative strategies, should be directed to endogenous and potentially reinforcable mechanisms that counter the genesis and progress of psychiatric disorders. An interesting idea would be studies that compare people particular resilient to stress to their more sensitive counterparts as regards the development of psychiatric disorders like depression.

Finally, there is little doubt that environmental, ecosystem and climate degradation is an indirect and direct threat to mental (and physical) health. Indeed, urban decay adversely affects stress-processing in brain regions implicated mental illness (Lederbogen et al., 2011). Conversely, a green and protected environment has repeatedly been shown to enhance well-being, even in an urban context, and will reduce the risk of psychiatric disorders like depression (Alcock et al., 2014; Astell-Burt et al., 2013; Nutsford et al., 2013; Richardson et al., 2013).

4.8. Correlated does not mean causal does not mean curative

Finally, a simple but important point that has been discussed elsewhere should be mentioned (Dean et al., 2013; Harrison, 2015; Millan, 2006, 2014b). The mere association of a readout like a genetic anomaly or increased tissue levels of a transmitter with a psychiatric disorder is not synonymous with a causal role: as implied in the previous paragraph, it may have the opposite significance or be merely an epiphenomemon (Millan, 2014b). Even if the link is causal (or protective) it does not necessarily hold that it is the most appropriate target for medication. For example, the mechanism in question may only be developmentally active during brain formation, or it may be inaccessible to pharmacological manipulation (Millan et al., 2012; Veenstra-VanderWeele and Warren, 2015). Hence, it cannot automatically be assumed that identifying the pathological substrates of psychiatric disorders and domains of dysfunction is tantamount to pinpointing the ideal target for their treatment.

5. Experimental study of psychiatric disorders: refining animal models (Table 3)

5.1. The challenge of animal models for psychiatric disorders: multi-hit paradigms

Over the years, the literature has been replete with hopeful claims of models *of* various psychiatric disorders, and the term can still widely be encountered (in many cases used unthinkingly, one suspects). However, there is a growing consensus that a more appropriate pronoun would be *for* (Carpenter and Koenig, 2008; Enna and Williams 2009; Insel, 2007; Jones et al., 2011; Kas et al., 2011a,b; Powell and Miyakawa, 2006; Marcou et al., 2009; Pratt et al., 2012). It is likely impossible to model an entire psychiatric disease *per se* and all the more so if we assume that psychiatric disorders embrace core, human-specific facets like verbal language (Burns, 2006; Dean, 2009; Millan et al, 2012). Conversely, it appears more feasible to model specific classes of symptom, pathophysiological mechanism, genetic risk factor or epigenetic anomaly etc. This has been referred to as a more "dimensional" *vs* "syndromic "approach to modelling psychiatric disorders, and it mirrors the above-mentioned "dimensional" approach to categorising psychiatric disorders themselves (Section 3) (Enna and Williams 2009; Jones et al., 2011; Kas et al., 2011a.b; Marcou et al., 2009; Papaleo et al., 2012; Schughart et al., 2013).

The challenges for models are well exemplified for schizophrenia where one might cite disruption of working memory, GABA/glutamatergic circuits, Neuregulin and DNA methylation as examples of, respectively, symptoms, pathophysiological mechanisms, genetic risk factors and epigenetic anomalies that can realistically be reproduced in rodents. Conversely, impairment of verbal language and disorganised thought may be pretty well intractable (Burns, 2006; Dean 2009; Grayson and Guidotti, 2012; Law et al., 2012; Millan et al., 2012; Papaleo et al., 2012; Powell and Miyakawa, 2006). In fact, for schizophrenia, there is a surprisingly rich palette of models now available reflecting a shift of focus from genetic to developmental paradigms. On the other hand, there has been less progress as regards new models for depression, bipolar disorder and anxiety disorders (Carpenter and Koenig, 2009; Enna and Williams 2009; Jones et al., 2011; Marcou et al., 2009; Réus et al., 2014).

While the human brain – like the eponymous brain coral and other ecological communities – is resilient to isolated stressors, recurrent exposure to multiple and divergent risk factors disrupts homoeostasis and triggers disease (Anthony et al., 2015; McClanahan et al., 2012; Millan, 2006; Roff and Mumby, 2012). Hence, models that manipulate only a *single* factor such as a risk gene remain of limited construct validity for modelling psychiatric disorders. One exception may be rodent models of high-penetrance CNVs which embrace multiple genetic hits and which can be well reproduced in mice by chromosome engineering due to their high degree of synteny (gene order) with humans: the above-mentioned 22q11 (Sections 4. 2) is a good example (Kirov et al., 2013; Millan, 2013; Nomura and Takumi, 2012; Doherty and Owen, 2014; Sigurdsson et al., 2010). Nonetheless, of broader interest are multi-hit models that take account of synergistic interactions amongst several risk factors. For example, they can mimic the impact of an environmental risk factor superimposed upon a vulnerable genetic background, such as adolescent psychosocial stress in mice with a disrupted risk gene (Neuregulin 1) for schizophrenia (Desbonnet et al., 2012; Hida et al., 2013; Kas et al., 2011a,b; Papaleo et al., 2012; Schughart et al., 2013).

Table 3 Overview of recent changes in thinking and performance of R&D for psychiatric disorders as concerns preclinical R and D, therapeutic concepts and treatment modalities.

Area of R and D	*Recent and future developments*
Experimental validation of hypotheses, targets and drug discovery for novel agents	Multi-hit models (gene, environment) *for* psychiatric disorders and domains of dysfunction, mirroring cumulative risk factors for patients. De-emphasis of models lacking face and construct validity. Specific manipulation of discrete proteins in a region, cell type and life-phase dependent manner (conditional KO, gene silencing, genome editing, optogenetics, etc). Longitudinal studies of phenotype throughout life: chronic drug administration during key periods like adolescence, with measurement of long-term effects. More sophisticated studies in mice, and extension to rats (e.g., transgenic lines). Specific procedures in species from zebrafish (CNS development) to prairie voles (social cognition). Greater efforts to independently corroborate key findings on targets and mechanisms, both precise replication (reproducibility) and studies under similar conditions (robustness). Novel incentives and procedures to facilitate publication of negative data and non-confirmatory findings. Basically all "pre-competitive" data to share. Greater analysis of individual variation in animals, like contrasting responses to treatments: resembles notion of personalized medicine for patients – insights into novel biomarkers. Back-translation of human neuroimaging, EEG and other findings into rodents and (if essential) primates. Studies to undertake in parallel with behavioural and neurochemical readouts to understand circuit pathophysiology. Phenotypic screening using integrated cellular/*in vivo* models for psychiatric disorders and pathophysiological processes, then de-convolution (reverse screening) to find drug targets. *In vitro* models for drug characterisation and screening: multiplexed functional readouts and high content imaging: from single cells to differentiated neural networks – for example, derived from human iPSC cells. Structure-based drug discovery based on improved crystal structures, better ligand purification, chemoinformatic modelling and higher quality medicinal chemistry (e.g. fragment-based design). Greater attention to false positives in assays due to, for example, interference by covalent reaction of ligand with target protein; ligand aggregation or degradation. Confirmation of hits with 2nd procedure.
Novel therapeutic concepts and modes of target exploitation	Correlated (gene/protein affected in a disorder) not synonymous with causal (trigger); causal not synonymous with cure, since impact may have passed (early life) or "target" undruggable. For every new target, not just selective agents but also multi-target ligands possessing complementary modes of action should be designed and evaluated in parallel. Multi-target and other strategies should be examined for circuit level actions on network plasticity, connectivity and resilience, etc. New modes of modulation for (known and orphan) GPCRs and ion channels *via* allosteric sites, inverse agonism, protein-partners, heterodimerisation, G-protein independent and biased signalling. Target untapped cellular mechanisms like epigenetic regulation, mitochondrial energetics, discrete kinases, neurotrophic factors, cell adhesion, gliotransmission and apoptosis etc. Drug repurposing: new functional properties and therapeutic actions for known and safe agents either in clinical use (reorientation) or abandoned (rescue).

Table 3 (*continued*)

Area of R and D	*Recent and future developments*
	In addition to small molecules, novel therapeutic strategies like passive antibodies and miRNA mimics/antagomirs: genome editing/genetic correction for monogenic disorders. From purely symptomatic to course-altering treatment to directly counter pathophysiological mechanisms: both rescue (e.g., ASD) and prevention (e.g., schizophrenia). Psychotherapy and brain stimulation techniques, both alone and coupled to pharmacotherapy for optimising therapeutic efficacy.

The table summarizes the points discussed in more detail in the text. ASD, autism-spectrum disorder; EEG, electroencephalography; GPCR, G-protein coupled receptor; iPSC, induced pluripotent stem cell; KO, knockout and miRNA, microRNA.

5.2. More focused, time and region-dependent manipulation of cerebral function

As regards gene-manipulation studies themselves, it is important to note progress relative to the traditional life-long, constitutive Knockout mouse. There are now greater possibilities for deleting and inducing genes at specific phases of life, and in discrete regions and cell types, and also for introducing humanised genes and even entire loci (Devoy et al., 2012). Such approaches can be complemented by local shRNA gene-silencing techniques, genomic editing ("CRISPR", "TALEN" and Zinc Finger Nuclease") and optogenetic manipulation of the activity of specific neurones, providing further insights into the role of discrete proteins, neural elements and circuits (Aston-Jones and Deisseroth, 2013; Carroll, 2013; Devoy et al., 2012; Gaj et al., 2013; Gamber, 2014; Jacob et al., 2010; Pardridge, 2007; Révy et al., 2014; Schmid and Haass, 2013). These techniques allow for more precision in the functional evaluation of potentially-relevant mechanisms for therapy, though it should not be forgotten that medication is not introduced into specific brain regions, but rather given systemically.

5.3. Timing of treatment, and the issue of gender

As regards drug administration, complementary to the acute injection of drugs in adult rats, there is a need for greater attention to their long-term effects (tolerance, sensitisation, withdrawal). A recent and encouraging tendency is to compare the impact of pharmacological agents during specific phases of life since actions and underlying pathophysiology may well differ (Arango, 2015). One topical example, related to the notion of preventing psychiatric disorders (Section 7.3), is to examine whether sustained adolescent treatment may impede the adult appearance of behavioural and neurochemical deficits in developmental models for schizophrenia (Clifton et al., 2013; Kas et al., 2011b). For drugs impacting biological or sleep rhythms, attention to the time of day is important: for example, the effects of melatonergic agents are very different when applied just before the dark as compared to light phase (Cardinali et al., 2012; De Bodinat et al., 2010; Owen, 2006). This factor should be more often considered in view of its relevance to the time of day at which patients take their medication.

Finally, while most studies are undertaken in males, they accounts for only about one half of human subjects, so the importance of not neglecting the factor of gender in animal studies of psychiatric disorders and their alleviation should be underscored (Kokras and Dalla, 2014).

5.4. Enriching the repertoire of behavioural readouts: integrating social cognition and ethology

The behavioural repertoire of rodents has not exactly evolved a great deal since the advent of neuropharmacology, and they still steadfastly refuse to tell us what they feel and think. Behavioural readouts are usually based on a motor response like locomotion or pedal-pressing. However, several new behavioural approaches justify mention.

First, the use of touch-screen procedures for interrogating cognitive processes has been back-translated from comparable protocols in humans (Dudchenko et al., 2012; Marcou et al., 2009; Talpos and Steckler, 2013). This is an example of the important principle, further accentuated below (Section 8) of optimising comparability between tests in animals on the one hand and those used in patients on the other.

Second, more attempts are being made to link behavioural readouts to their neurochemical, electrophysiological and neuroanatomical substrates in order to understand the neurobiological causes of anomalies. Readouts employed like extracellular glutamate levels, stimulus-evoked electrophysiological responses and circuit neuroimaging can all be translationally performed in humans (Buckholtz and Meyer-Lindenberg, 2012; English et al., 2014; Gobert et al., 2011; Poels et al., 2014).

Third, there is increasing attention to the sound-world of rodents themselves, namely response to – and emission of – ultrasonic vocalisations in the context of sexual behaviour, adolescent play and social interaction (Scattoni et al., 2009; Millan and Bales 2013; Panksepp, 2010).

Fourth, impaired social processing/cognition is closely linked to patient dysfunction in disorders like schizophrenia and ASD (Brüne and Brüne-Cohrs, 2006; Hoertnagl and Hofer, 2014; Foussias et al., 2014; Millan et al., 2012, 2014). Hence, efforts are being made to improve its study in rodent models, though this remains a difficult task. Most work has focused on social recognition, and various ways of manipulating social interaction, itself a complex construct (De Jaegher et al., 2010; Millan and Bales, 2013; Wilson and Koenig, 2014). In fact, fully-fledged social cognition (theory of mind and emotional processing) is probably not present in rodents underpinning the quest for alternative species for its study (Brüne and Brüne-Cohrs, 2006; Millan et al., 2012). The most appropriate would be apes and,

reflecting convergent evolution, Corvids (crow family), dolphins and elephants (Brüne and Brüne-Cohrs, 2006; Emery and Clayton, 2004, 2009; Hart et al., 2008; Millan et al., 2012). Despite the potential use of primates for some specialised studies, their use must be minimised (Millan and Bales, 2013) while apes and the other species mentioned are obviously neither practical nor ethically-acceptable candidates! On the other hand, studies of pair bonding in prairie voles have proven instructive, notably as regards the roles of oxytocin, vasopressin and DA (Blumstein et al., 2010; McGraw and Young, 2010; Wang et al., 2013). Much remains to be learned about endogenous mechanisms that modulate social processing, and their perturbation in psychiatric disorders, as a basis for devising novel therapeutic strategies for restoration (Insel, 2007; Meyer-Lindenberg et al., 2011; Millan and Bales, 2013). Social cognition/processing exemplifies the old adage that the best experimental model is humans and important insights into its modulation by oxytocin have emerged from studies in healthy volunteers as well as patients with schizophrenia and ASD (Insel, 2007; Meyer-Lindenberg et al., 2011; Perez-Rodriguez et al., 2014).

Finally, along these lines, an ethological approach consisting of the observation of undisturbed animals under naturalistic conditions may be informative for revealing subtle alterations in affect and cognition related to psychiatric disorders (Greggor et al., 2014; Hånell and Marklund, 2014; Hofmann et al., 2014). Such studies could be undertaken with a variety of conditions known to impact emotional and cognitive operations, during both active and sleep phases, with animals alone and socially interacting, and following genetic and/or environmental manipulations that mimic risk factors for psychiatric disorders (Blumstein et al., 2010; Buchanan et al., 2013; Hofmann et al., 2014). They may lead to more ethologically-founded and real-world relevant models of greater sensitivity to the effects of potential treatments than conventional, experimental procedures currently in use.

5.5. Reproducibility; inter-individual differences and genuine exploratory research: key issues

There are three other issues concerning *in vivo* and *in vitro* studies that warrant brief mention.

First, in common with many fields of R&D, there is a need for more rigorous confirmation of novel preclinical observations, especially concerning putative new drug targets and pathophysiological mechanisms underpinning psychiatric disorders (Ioannidis, 2005, 2014; Prinz et al., 2011; Ségalat, 2010; Steckler, 2015). This is especially true when they are unveiled by studies of sometimes Byzantine complexity employing a palette of high-tech techniques. It is crucial to establish: *Reproducibility* of findings when precisely re-performed; *robustness* of conclusions when confirmed under similar but not identical conditions; and the genuine *relevance* of observations to CNS disorders in humans and their treatment as established by a broad suite of preclinical and (where possible) clinical studies. An important issue is, amongst others, the rigorous statistical design and powering of studies. Obviously, the reliability of clinical data, such as those emanating from genetic studies, is also of paramount importance (Muglia, 2011; Lazzeroni et al., 2014).

Second, despite the inviolate deity of statistical significance for determining genuine differences amongst experimental groups, there is a need to understand rather than ignore differences between individuals. As regards, for example, their genetic and epigenetic underpinnings, and differences in personality (Castro et al., 2012; Hommers et al., 2015; Kas et al., 2011b; Réale et al., 2007; Verheij and Cools, 2008). Inter-individual differences can provide a lot of usually neglected yet important information and, mirroring ethological work, their analysis in the course of long-term, longitudinal studies commencing in development would be of particular interest (Clutton-Brock and Sheldon, 2010; Kas et al., 2011a). Moreover, their pertinence to the current preoccupation with personalised medicine in humans is obvious, but has yet to be explored (Section 8.5).

Third, the current mantra decrees that the translatability of animal data to humans is of primordial importance and, indeed, as outlined below (Section 8.2), this is a crucial element for progress in drug development. Nonetheless, not everything can nor needs to be translated. More generally, the emphasis on translation (from funding to publication) should not be allowed to detract from the importance of basic, no-strings-attached, focused and even off-beat research in the domain of psychiatric disorders, even without any concrete notions of clinical relevance or application, and on topics and mechanisms not currently *en vogue*. Without fostering such fundamental research, we incur the risk that at some point there will be nothing left to translate (Minogue, and Wolinsky, 2010; Weinberg, 2010). In this regard, it is critical to remain flexible, open-minded and reactive in early-phase exploratory research. Despite the desire and need to structure and channel ideas and to predict future (budgetary etc) requirements, it is important to resist the over-programming and counterproductive control of budding ideas, research and experimentation (Applbaum, 2009).

6. Cellular procedures for drug characterisation and discovery (Table 3)

6.1. Target-based molecular characterisation and High-Throughput Screening

Though target-based drug discovery was for many years dependent on binding studies effected on native tissue and/or the use of isolated organs, the emergence of molecular biology in the late 1980s led to a predilection for studies of recombinant human proteins (receptors, transporters, enzymes, etc.) transfected one at a time into simple cellular expression systems like CHO and HEK cells. This allowed for the target in question to be studied in isolation, and for drugs to be identified and characterised without interference from other proteins with which they might potentially interact (Enna and Williams, 2009; Maccaron et al., 2011; Sams-Dodd, 2013). Simple readouts were usually employed like binding affinities, cAMP accumulation or global levels of G protein. This work-horse of cellular pharmacology has served as an invaluable set-up for first-line ligand characterisation and drug discovery driven by medicinal chemistry. It has also been exploited (with somewhat less success it must be said) as a core platform for HTS

Procedures dedicated to the identification of novel ligands for new targets, often coupled to the screening of ever more extensive libraries (Comley, 2014; Maccaron et al., 2011; Sams-Dodd, 2013; Swinney and Anthony, 2011).

In any event, simple cellular systems are far removed from the natural environment of receptors and other biological proteins, and drugs may act in the brain in a manner very different to their behaviour at purified membranes as determined by just one parameter. For example, many GPCRs engage multiple signalling pathways and their properties are modified by interactions with other proteins, including other classes of GPCR (Enna and Williams, 2009; Heilker et al., 2009; Maccaron et al., 2011; Terstappen et al., 2007). Hence, there is now a preference to study recombinant and endogenous populations of proteins in neuronal (or glial) cells using multiple readouts of drug activity, and to relate observations to findings in, for example, primary cell cultures and cerebral tissue. As regards HTS screening, this has likewise progressed with multiple readouts (multiplexing), closer attention to drug efficacies *vs* mere affinities and high-content analysis including fluorescent-based technologies and whole-cell imaging (Comley, 2014; Cotton et al., 2013; Neuzil et al., 2012; Zhu et al., 2014). In addition, chemistry has renounced the illusory gains of combinatorial chemistry, it is enriched by fragment- and antibody-based design, and is underpinned by more refined structural (crystallography) analyses of drug-protein interactions (Bottegoni et al., 2011; Hubbard, 2011; Keseru and Makara, 2009; Lawson, 2012; Maccaron et al., 2011).

Virtual screening (algorithms used to identify and predict novel bioactive compounds in the hit to lead phase) as well as *in silico* analysis of structure–activity-relationships are more sophisticated in several ways. They now can, for example: exploit machine-learning techniques to refine the design of new chemical structures; benefit from improved insights into protein-folding and the dynamics of macromolecular complexes; integrate the roles of water molecules; and better predict genuine drug-like properties (Bottegoni et al., 2011; Gabrielsson et al., 2009; Hubbard, 2011; Keiser et al., 2009; Khatib et al., 2011; Lee et al., 2011; Schneider, 2010; Wager et al., 2010). Models will never be enough alone, but their predictions are increasingly converging with the actual syntheses of "wet" chemistry.

Finally, there is more attention to the risks of false positives which are no less a danger for drug screens than false negatives: both can have heavy consequences. Compounds yielding false positive responses lurk systematically in certain types of chemical structure and can confuse readouts and interpretation by, for example, disrupting membranes, aggregating, sequestering metal cofactors for enzymes and covalently modifying target proteins etc. They may represent up to 10% of ligands in a standard academic library and are best teased out by the use of multiple assays and readouts (Baell and Walters, 2014; Cotton et al., 2013; Dahlin and Walters, 2014).

6.2. Phenotypic screening using integrated cellular networks and simple model organisms

In recent years, mirroring interest in neural circuits, "Network Pharmacology" and "Systems biology" (Galizzi et al., 2013; Kotaleski and Blackwell, 2010; Mei et al., 2012; Nussinov et al., 2011; Phillips et al., 2012; Silverman and Loscalzo, 2012), there has been a move towards phenotypic screening. That is, studies of biological actions performed in integrated systems rather than on single cells/proteins, and using a diversity of functional readouts from cellular signalling to neuritic outgrowth to synaptic transmission to (*in vivo*) behaviour (Grabrucker et al., 2013; Lee et al., 2011; Penrod et al., 2011; Sams-Dodd, 2013; Swinney, 2014; Swinney and Anthony, 2011; Winchester et al., 2014). Although such studies can be performed under physiological conditions, the ability of agents to normalise a functional deficit is of greater interest.

Phenotypic screening is usually performed in a hypothesis-free manner (reminiscent of GWAS) to identify active compounds. Then, by a process of "deconvolution" their mechanisms of action can be identified and drug-like properties refined with further chemistry (Lee et al., 2011; Swinney, 2014; Swinney and Anthony, 2011; Terstappen et al., 2007). This type of phenotypic screening can be performed both with new chemical entities and with known and safe compounds intended for repurposing (Section 6.3).

The phenotypic approach is actually akin to traditional behavioural screening – Janssen systematically evaluated the neuroleptic potential of essentially all compounds in rodents in the epoch of haloperidol. However, a broader suite of technologies is now available, with greater possibilities for identifying the cellular substrates of drug actions. Dependent upon the disorder and pathophysiology of interest, many different models might be privileged. These include primary cell cultures from genetic mouse models of psychiatric disorders, as well as induced pluripotent stem cells (iPSCs) obtained from patients and differentiated into neuronal networks (Inoue and Yamanaka, 2011; Maury et al., 2011; Vaccarino et al., 2011). This iPSC line of research is particularly dynamic with, for example, the recent demonstration that iPSCs can be coaxed into forming 3D cultures *in vivo* with properties closer to *in vivo* networks than standard 2D cultures, and that they can integrate with endogenous circuits following transplantation into mouse brain (Choi et al., 2014; Espuny-Camacho et al., 2013; Jacob et al., 2010). Neurally-differentiated iPSCs allow for the investigation of the cellular phenotypes of patients with defined genetic and clinical features. Though most data have been generated using iPSCs from patients with monogenic forms of ASD-related disorder, the first attempts to model schizophrenia were recently reported (Bray et al., 2012). Another intriguing approach is to generate neuronal networks from cells derived from the nasal epithelium (Benitez-King et al., 2011).

Of potential importance are also the well-characterised, non-vertebrate model systems: Caenorhabdis elegans (nematode) (Wang et al., 2011) and Drosophila melanogaster (fruit-fly) (Van Alphen and van Swinderen, 2013). In addition, procedures relevant to psychiatric disorders are currently under exploration in zebrafish. Despite obvious limitations, their transparent larvae are well-adapted to studies of developmental processes – like neuronal migration – perturbed in schizophrenia and ASD (Norton, 2013; Schmid and Haass, 2013): see also Kas et al. (2011a) and Sokolowski (2010).

As compared to conventional HTS programmes focused on a single target, phenotypic strategies are inherently more broad-minded and implicitly take into account a plurality of MOAs. Hence, while HTS programmes tend to ignore and eliminate any interaction other than the one targeted, phenotypic strategies

are more likely to detect and pursue agents with unexpected actions and/or multi-modal profiles (Section 7.1) (Galizzi et al., 2013; Hasan et al., 2012; Mei et al., 2012).

Finally, a risk of phenotypic strategies is the inability to clearly define a drug mechanism of action.

6.3. Drug repurposing: rescue and reorientation

An increasingly prevalent idea in many fields of medicine – such as oncology – is drug repurposing. This refers to a process whereby a clinically-used drug (re-orientation/therapeutic switching) or discontinued agent (rescue) is re-characterised *mechanistically* in *experimental* then clinical paradigms and shown to possess hitherto-unknown properties of potential use in an alternative disorder (Cavalla, 2009; Green and Hudson-Farmer, 2013; Hasan et al., 2012; Keiser et al., 2009; Oprea et al., 2011). Repurposing assumes that the agent is safe and that new patents can be taken to protect its novel niche (Oprea et al., 2011; Smith, 2011). As compared to new chemical entities and new drug applications, a repurposing strategy may gain considerable time (and expense) in getting novel therapies to patients (Cavalla, 2009; Green and Hudson-Farmer, 2013). Repurposing can be promoted by re-evaluating agents for previously-ignored polypharmacology, by phenotypic screening and by network modelling (Keiser et al., 2009; Mei et al., 2012; Reaume, 2011).

In fact, as related above (and apparent from Table 1), the history of psychotropic agents includes many examples where drugs have been re-oriented from one initial indication to another. Indeed, the clinicians who, in the 1950s, discovered the first wave of psychotropic agents were arguably pioneers in this respect! (Section 2). More recently, the use of antipsychotics and anticonvulsants to treat bipolar disorder, and of SSRIs to control OCD and anxiety disorders, offer further examples of repurposing. Another good example is the antibiotic minocycline which is under investigation for the treatment of schizophrenia (Chaudhry et al., 2012; Millan et al., 2014; Muthyala, 2011).

Drug repurposing can be aided by programmes of experimental medicine whereby, for unmarketed drugs known to be safe, studies can be performed in healthy subjects using a range of neuroimaging, endocrine, EEG and cognitive readouts etc (Insel, 2007; Mullard, 2011; Schumann et al., 2014). Experimental medicine embraces both drugs to be repurposed themselves, as well as those acting selectively at discrete targets in order to better understand their functional significance and therapeutic relevance. It may also be extended to non-pharmacotherapeutic treatments used in association with medication (Browning et al., 2011).

It is worth pointing out both the ECNP (Medicine Chest) and the NIH (Medicine Cabinet) are sponsoring initiatives to make drugs that will not be developed commercially-available to academia and clinical investigators. Further, drug repurposing is a key element of the NIH's initiative to foster improved translational research (Downs and Blackburn, 2012; Marcou et al., 2009; Oprea et al., 2011).

7. Novel pharmacotherapeutic concepts and modes of target manipulation (Table 3)

Not only the *way* in which new medication is being discovered is evolving, in addition the nature of *what* is being sought is changing.

7.1. Multi-target and other network-driven strategies.

Either directly or indirectly, currently-available medication for treating psychiatric disorders exerts a widespread influence on cerebral networks controlling mood and

Table 4 Overview of recent changes in thinking and performance of R&D for psychiatric disorders as concerns their clinical development and the overall organisation of R and D

Area of R and D	*Recent and future developments*
Clinical evaluation and utilisation of novel medication	Improved translational linking of preclinical to clinical work *via* common readouts and procedures. Back-translation of human findings to animals to refine models and measures. Better validation of medication target-engagement *prior* to Proof of Concept studies by use of PK/PD studies and multimodal neuroimaging, EEG etc. More thorough characterisation of subjects for early human studies: clinical and biomarker. Where possible, open, exploratory studies in patients by skilled and insightful physicians for determining potential clinical utility of compounds with novel mechanisms of action. Revised and refined rating scales; diverse measures of real-world function; complementary patient, carer and physician assessments for more comprehensive picture of treatment efficacy. Together with regulators, setting up of novel (and adaptive) trial designs for testing innovative mechanisms of action and measuring distinct therapeutic outcomes in specific populations. Commence trials in small, target populations stratified by common clinical profiles and/or biomarkers of the symptom/pathophysiological mechanism targeted by drug. Thereafter, broader populations.

Table 4 (*continued*)

Area of R and D	*Recent and future developments*
	Initiate development in a homogeneous, well-defined disorder like Fragile X before moving to more heterogeneous and prevalent diseases like sporadic ASD and schizophrenia. Optimise designs for demonstrating superiority to existing medication: comparator trials, evaluation in resistant subjects, switching, testing as add-on for improved efficacy. Focus on evidence and needs-based medicine. Personalized and precision medicine are long-term goals for the future, not yet feasible nor affordable. Improve compliance (clinical trials and after launch) by more convenient/less frequent dosing, excellent tolerance, remote monitoring, family implication, psychoeducation….. Digital health/e-medicine: Internet/PC/Smart-App driven patient data-sharing, consultation, treatment, identification (pharmacogenomic) and monitoring; e.g., remote following of patient behaviour and sleep in real time. Novel trial designs.
Organisation of R & D, and collaboration between various partners	Major national and supranational efforts to promote therapeutic progress/drug discovery for psychiatric disorders, notably IMI. Pre-competitive collaborations on, for example, new translational tools and experimental models. Industry, despite internal reduction in R&D, searching for partnerships with Biotech and Academia: high interest for licencing-in and developing agents from other sources. Academia more oriented towards clinical and socio-economic relevance of research coupled to IP protection: moves to drug discovery and collaboration with Industry. Sustained funding required to forward translational research. New modes of collaboration between Industry and Academia such as "Open Innovation": access of Academia to Pharma chemical libraries, screening procedures and lab space. Data sharing and analysis. New skills/joint training programmes to enhance partnership efficacy. Collaborations and consultation meeting uniting all key actors – regulators, industry, academia, clinicians and patients: organised by IMI, EMA and ECNP, for example Greater implication of better-informed patients and patient communities: enhancement of patient alliances with therapists, definition of real-world patient needs, setting up of research programmes and optimal trial designs etc. Clinical populations for new compounds more confined but better defined: drugs should be more efficacious (reasonable reimbursement). Niche markets *vs* blockbuster model. Global thinking for mental health. Specificities of other cultures in terms of patients and trial design. Extension of future progress to less affluent regions coupled to basic health-care and socio-economic, public hygiene and environmental (protection/preservation) policies. Big data generation, storing, sharing and analysis (GWAS, genome-sequencing, brain-mapping, connectomics, mobile health data, etc): needs new and effective solutions for all actors in R&D. Improve and extend IP protection for innovative treatment strategies. Ensure long-term future of R&D for brain disorders. Experience, expertise and knowledge must not be lost but passed on: depends upon active research and creation of permanent public and private jobs for a new wave of bright, motivated and well-trained young people.

The table summarizes the points discussed in more detail in the text. ASD, Autism-Spectrum Disorder; ECNP; European College of Neuropsychopharmacology; EMA, European Medicines Agency; GWAS, Genome-Wide Association Study; IMI, Innovative Medicines Initiative; IP, Intellectual property; MOA, Mechanism of action; NCATS, National Centre for Translational Science; PK/PD, Pharmacokinetics/Pharmacodynamics; POC, Proof of Concept and R and D, Research and development.

cognition. Even SSRIs generally have some additional interactions (such as 5-HT2C receptors, nicotinic receptors and sigma1 sites) and release 5-HT onto 14 classes of receptor broadly distributed in the CNS (Artigas, 2013; Millan, 2006). It is, thus, noteworthy that for the last 20 years or so, despite increasing awareness of the complexity of CNS

disorders, the emphasis in drug discovery has been on extreme selectivity and high potency in the search for more efficacious agents acting at "novel targets". For example, as regards a diversity of receptors for neuropeptides evaluated in depression, anxiety and/or schizophrenia, none of which revealed clinical activity sufficiently robust for authorisation (Sections 2.3.4. and 2.5.2.). Arguably, the targets are clinically relevant but selective agents are not sufficiently powerful *alone*, so activity would better be exploited in combination with other mechanisms of action (Millan, 2006, 2009, 2014a).

Even today, the predilection with selectivity remains strongly enrooted, and almost all target-driven drug discovery programmes are initiated without the question even being asked of whether a selective agent (apart from its utility as a tool) is really what is clinically required (Bottegoni et al., 2011; Huggins et al., 2012; Keseru and Makara, 2009; Müller-Schiffman et al., 2010). Nonetheless, and in line with network thinking, there is growing interest in multi-target strategies for re-equilibrating perturbed circuits. While an agent acting at a key network hub like GABAergic interneurones may be effective, the union of several, complementary mechanisms of action is better adapted to control multi-factorial and multi-symptom psychiatric disorders as exemplified by clozapine and schizophrenia (Millan, 2006; Wong et al., 2010). Two mechanisms of action can be coupled together either in a single compound or associated by the use of two separate agents: the pros and cons of multi-target agents *vs* drug associations have been comprehensively analysed elsewhere (Ballon and Stroup, 2013; Millan, 2014a).

For innovative targets, it would seem wise to develop both selective *and* multi-target drugs, and to consider upfront possible strategies of clinical association. All three potential therapeutic solutions require preclinical evaluation. In the course of screening, unforeseen activities inevitably crop up: rather than their systematic exclusion, those of potential therapeutic utility should be reinforced, whereas those linked to adverse actions should be deleted.

7.2. The search for innovative targets and novel concepts: beyond me too

The terms "me-too" or "me-better" are used to refer (in most cases disparagingly) to new agents differing more quantitatively than qualitatively to their predecessors (Carpenter and Koenig, 2008; Zhao and Guo, 2009). No two drugs are identical and each will have its advantages and disadvantages (Millan, 2006). However, they have to be proven. Further, though me-better obviously implies progress, it is not always clear how much and for whom, while me-too implicitly suggests nothing much very new. Currently, there is a reluctance to see more additions to families of SGAs and SSRIs, for example, as would be reflected in the attribution of a very low level of reimbursement – assuming no unforeseen and clinically-proven gain in efficacy. Rather, there is a just and understandable desire for innovation, assuming that it is coupled to therapeutic progress and improved patient real-world function (Carpenter and Koenig, 2008). In fact, at the inception of a drug-discovery project *nobody* is thinking me-too in reality, and the situation is not quite as black and white as it may at first sight seem.

Imagine that a novel and validated target is exploited by one single company who bring to Phase III or even market an excellent agent which suddenly has to be withdrawn for an unanticipated safety issue. Should no back-up be available in the same company, and no other firm active on the target, then the therapeutic novelty would be essentially lost – or the whole programme would need to be restarted from scratch. Conversely, if several groups are working on the target in parallel, even if there is a problem with the first agent to reach the clinic, other agents should soon fill the gap and become available to patients. *A priori*, it is impossible to know at the outset which project-compound is the most likely to succeed and to have the best profile. All this may happen concurrently over a time scale of 10-20 years and, in this respect, the criticism that companies are looking for me-too mimics seems a trifle unfair. From the patient's perspective, for a genuinely important target-concept, it would seem wise to keep several irons in the fire in order to ensure that at least one will become available to them in a reasonable time-frame.

Nonetheless, as stated above, there are clear limits to the desire and need to produce an endless succession of new drugs acting with similar mechanisms of action. Hence, the question remains of which genuinely innovative drug targets might lead to greater efficacy and therapeutic range in the management of psychiatric disorders. Sequencing the human genome did not unleash a cascade of novel, high quality, accessible and validated targets, and there is no simple answer to this question (Drews, 2003, 2006; Rask-Andersen et al., 2011; Swinney and Anthony, 2011). The following points are, however, of relevance.

GPCRs and ion channel-coupled receptors still retain their attraction yet, in addition to those harnessed by conventional transmitters and neuromediators, orphan GPCRs and other unexploited classes are under scrutiny with more potential modes of modulation than in the past. They include: 1), inverse agonists; 2), allosteric ligands for fine tuning signalling and offering novel chemical pistes: 3), biased transduction by drugs that act only *via* discrete signalling pathways: 4), manipulation of G-protein-independent signalling; 5), GPCR-interacting proteins and 6), drugs preferentially recognising heterodimeric assemblies *vs* monomers/dimers (Chico et al., 2009; Conn et al., 2014; Dimond et al., 2011; Duman and Voleti, 2012; Hounsou et al., 2014; Maurice et al., 2011; Nussinov et al., 2011; Swinney and Anthony, 2011).

In addition to epigenetic regulation (Section 4.3), many as yet unexploited cellular processes are attracting interest for the treatment of psychiatric disorders like: axonal dynamics and dendritogenesis; mitochondrial energy supply; neuroinflammation, glial transmission; myelination; cell adhesion and apoptosis (Araque et al., 2014; Clay et al., 2011; Czeh and Di Benedetto, 2012; Glausier and Lewis, 2013; Grabucker et al., 2013; Kofink et al., 2013; Millan, 2013; Reichelt et al., 2012; Ren et al., 2013; Südhof, 2012; Fossat et al., 2012; Winchester et al., 2014). Many of these processes are confined to specific cellular compartments so the notion of intracellular targeting should also be evoked: drugs may need not only to get to the right cell, but also to the right place in the right cell (Miyashiro et al., 2009).

This is all highly promising, some potential challenges being: the potential dilution of limited resources in simultaneously trying to cover numerous *potentially* important targets; the

need for patient, rigorous and independent verification of hypotheses; biomarkers for identification of patient sub-populations possessing the relevant pathology (Section 8.2) and, in certain cases, the requirement to contact Regulators in advance to discuss novel and potentially-complicated clinical developmental paths (Section 8.4).

7.3. From symptomatic treatment to course-alteration: a potential paradigm shift

While all currently-available medication (as far as we know) acts symptomatically, there is increasing interest in strategies that may durably modify the progression of psychiatric disorders by interfering with underlying neurobiological anomalies, preferably prior to diagnosis, or soon after symptom manifestation (Fusar-Poli et al., 2013; Mueser and Cook, 2014; Sabbag et al., 2011; Veenstra-VanderWeele and Warren, 2015). This notion is partly driven by neurological disorders for which (or so we have been told) there is a pretty clear idea of core pathophysiological mechanisms (Cummings, 2009; Jack et al., 2013; Risacher and Saykin, 2013; Spillantini and Goedert, 2013). Further, it is being spearheaded by work with monogenic forms of ASD-related disorder where it is hoped that abnormal phenotypes can be rescued by appropriate interventions: for example, glutamatergic and GABAergic ligands for Fragile X, and replacement therapy for Rett Syndrome (Ehninger et al., 2008; Guy et al., 2007; Lozano et al., 2014; Pop et al., 2014). Increasing knowledge of aberrant developmental events and peri-adolescent risk factors leading to schizophrenia underlie intensive studies of young, high-risk patients and ways in which transition might be impeded (Fusar-Poli et al., 2013; Sabbag et al., 2011; Zipursky et al., 2013). Economic benefits of prevention and early treatment of psychiatric disorders are well recognised (Mihalopoulos et al., 2011) and, with increasing public and governmental awareness of the severe burden of mental health problems in the young (Murray et al., 2010), strategies aiming for course-alteration, early intervention and prevention will likely become more prominent in the future (Lee et al., 2014; Mueser and Cook, 2014).

The importance of non-pharmacotherapeutic strategies should also be underlined (Section 8.6), including psychotherapy which is specifically recommended in many countries for first-line treatment of adolescents at risk of conversion to schizophrenia (Fusar-Poli et al., 2013).

7.4. Novel modalities of therapeutic agent

Small molecules, derived from *de novo* chemistry and natural substances, continue to be the mainstay for innovative CNS drug discovery (Blazer and Neubig, 2009; Li and Vederas, 2009; Sarris et al., 2011; Zhao and Guo, 2009) but the emergence of other types of therapeutic agent, with oncology leading the way, should be mentioned. The general idea is to broaden therapeutic opportunities and to modulate otherwise un-druggable pathological mechanisms by use of, for example: 1), stabilised, small-interfering RNAs and DNA-directed interfering RNAs for specific gene silencing; 2), mimics and antagonists (antagomirs) of microRNA to regulate aberrant mRNA translation; 3) lipopeptides as novel modulators of GPCRs; 4), oligopeptides to disrupt abnormal protein-protein interactions: 5), aptamers (single-stranded, oligonucleotides that bind to proteins or nucleic acids) and 6), passive antibodies and even active immunisation to neutralise toxic proteins and drugs of abuse (Blazer and Neubig, 2009; De Souza et al., 2009; Dimond et al., 2011; Houslay, 2009; Keefe et al., 2010; Kinsey, 2014; Moreno and Janda, 2009; Suhy, 2014). Adenovirus-driven gene transfer and cell transplants, including genome-edited iPSCs, should also be mentioned (Maeder and Bumcrot, 2014; Mingozzi and High, 2011).

These strategies may well be very light-years away from first-line use in, say, the symptomatic treatment of major depression but, in a more realistic time-frame, they could be applied to resistant patients with well-defined pathologies (Schlaepfer et al., 2012), and monogenic forms of ASD-related, neurodevelopmental disorders (Millan, 2013). Hence, their rapid progress is well worth following.

8. Clinical development of novel medication: constraints and opportunities (Table 4)

8.1. The challenge of clinically developing novel agents for CNS disorders

Despite certain important successes, clinical trials for psychiatric disorders show a high attrition rate. Their complexity, length and cost, increasing placebo-response, frequent failure to obtain Phase IIb Proof of Concept or, when successful, difficulties to confirm findings in larger Phase III trials, have proven frustrating over the last decades (Chandler, 2013; Pammolli et al., 2011; Skripka-Serry, 2013). This can lead not only to rejection of the compound (and even therapeutic concept) under study but also, and more insidiously, to questioning of the predictive value of preclinical animal models. Further, additional requirements like the need in the EU for a (pre or post-authorisation) paediatric study, even if well-intended and of long-term benefit, have added further expense and challenges to clinical development (Arango, 2015; Eichler et al., 2013; Millan et al., 2015; Stoyanova-Beninska et al., 2011; Van Riet-Nales et al., 2014). This has been taking place in an unfavourable economic climate, and a legal and health service environment where patent protection is of limited duration, the clinical population to be treated will likely be more confined than in the past, and the negotiation of reimbursement with national pricing agencies is increasingly protracted.

Since many previous articles have focused on these issues, the following paragraphs and Section 9 focus on some recent and more positive developments which offer hope for a renewed dynamic in the development of novel agents for managing CNS disorders.

8.2. Translational linking of preclinical to clinical studies: new developments

An important element in the preparation and conduct of an efficient and informative therapeutic trial is the optimal linking of preclinical and clinical studies. This problem of a preclinical-clinical disconnect and the need for better "translation" has been underlined in innumerable articles. Further, as likewise discussed elsewhere (English et al., 2014; GENDEP Investigators et al., 2013; Risacher and Saykin, 2013; Scarr et al., in press),

there is increasing interest in biomarkers for both (1), identifying the most relevant patient subpopulations for study and (2), for tracking and predicting drug efficacy.

In fact, the current desire to better align experimental work with therapeutic studies is hardly a revelation, and has been a feature of clinical development since the inception of neuropsychopharmacology. Rather, it is a procedural revision inasmuch as more powerful and better-characterised tools are now available, like EEG and neuroimaging for achieving this goal (Borsook et al., 2011; Buckholtz and Meyer-Lindenberg, 2012; English et al., 2014; Fu and Costafreda, 2013; Schwarz et al., 2011). In addition, the Touch-Screen system for evaluating cognitive performance exemplifies a more rigorous conception of translational in terms of procedures, functional domains and readouts that are *identical* or as similar as possible between experimental species and patients (Dudchenko et al., 2012; Marcou et al., 2009; Talpos and Steckler, 2013). To optimise demonstration of target-engagement, translational research is increasingly being coupled to Pharmacokinetic/Pharmacodynamic (PK/PD) measures of drug exposure (Gabrielsson et al., 2009; Gelenberg et al., 2008). Animal models and procedures are being increasingly refined (Section 3) in a translational spirit to enhance their ability to predict therapeutic properties of new agents in patients. This task will always remain challenging but animals models at the very least are indispensable aids for selecting the appropriate doses of novel agents to be tested in Proof of Concept studies in patients.

Computerised modelling is routinely used to support programmes of screening coupled to HTS, and to characterise the properties and operation of cerebral and cellular circuits (Deco and Kringelbach, 2014; Kotaleski and Blackwell, 2010; Mei et al., 2012; Schneider, 2010; Fornito and Bullmore, 2015). Now it is being applied in a translational framework to predict the beneficial and adverse effects of novel drugs in humans. "Quantitative Systems Pharmacology" exploits preclinical data from *in vitro*/*in vivo* studies together with human neuroanatomical and imaging observations to model the influence of selective and multi-target drugs on neural networks, and hence to predict therapeutic efficacy and side-effects in early clinical trials (Geerts, 2011; Geerts et al., 2012; Huang et al., 2011; Schneider, 2010). One example is provided by the 5-HT2C agonist, vabicaserin. This potential antipsychotic was designed to reduce excess DA release in the limbic system. Modeling successfully predicted that the dose of vabicaserin used would not yield a sufficiently strong therapeutic response (Liu et al., 2014; Shen et al., 2011). Progressive fine-tuning of such models should prove increasingly useful in optimizing transition of new drugs to humans and in optimizing doses for target engagement and therapeutic efficacy. Another recently-described application is in the prediction of outcome for patients on placebo (Pilla Reddy et al., 2012).

Importantly, several broad-based initiatives have been introduced to foster the development of translational studies, such as the National Centre for Translational Research in the US and the NewMeds (Novel Methods leading to new medications in depression and schizophrenia) Innovative Medicines Initiative (IMI) consortium in the EU (Goldman, 2012; Khanna, 2012; Oprea et al., 2011; Slusher et al., 2013).

These new efforts to better bridge the preclinical-clinical gap should offer give a greater chance to novel medication to be evaluated at appropriate doses, under appropriate conditions, with appropriate readouts and in appropriate patients.

In view of the broad utilisation and rapid expansion of neuroimaging techniques, the following paragraph focuses on their use in the service of translational studies.

8.3. Translational imaging at the systems level for facilitating clinical development

Neuroimaging has revolutionised human cognitive neuroscience as applied to psychiatric disorders but has not yet come into its own as a mainstay of methods for translational medicine. Several strategies to achieve this goal are being pursued which are relevant to other aspects of clinical development like personalised medicine (Section 8.5) and the refinement of animal models (Section 3).

First, neuroimaging, especially magnetic resonance imaging (MRI) based methods are devoting more attention to the core requirements of drug development such as reliability, cost, scalability and multi-site consistency. Encouragingly, several groups have designed cognitive and structural imaging tasks together with analysis algorithms that fulfil many of these demands (Borsook et al., 2011; Plichta et al., 2012).

Second, if genetic or environmental predictors are used to stratify participant populations, there is currently no objective way of inferring their systems-level correlates, limiting translational utility. Computational approaches may help advance understanding here. One example concerns their application to the impact of the rs4680 Catechol-O-Methyl Transferase (COMT) variant on dopaminergic regulation of the prefrontal cortex (Durstewitz and Seamans, 2008). COMT is a protein that catabolises DA and the gene exists in two variants, met and val, that respectively are less and more efficient in clearing DA (Chen et al., 2004). A biophysically-realistic model might better relate the relevance of this genetic variant to DA signalling, frontocortical circuitry and cognition, and might also help predict the actions of therapeutic agents. The Human Brain Project is a large scale programme in Europe that is moving towards this goal of comprehensive brain modelling and prediction of the actions of medication (Hampton, 2014). A rather less gargantuan and more focused application of computational neuroscience to psychiatry and therapeutic progress has been discussed elsewhere under the rubric "computational psychiatry" (Deco and Kringelbach, 2014; Montague et al., 2012; Wang and Krystal, 2014).

Third, understanding neural risk mechanisms using neuroimaging can help in the prospective personalisation of existing therapy. An example is again provided by the COMT rs4680 variant. The reduced prefrontal efficiency of DA signalling associated with the rs4680 val allele predicts that subjects carrying this variant should most profit from stimulation of dopaminergic transmission. This is what has been observed upon administration of the brain tissue-penetrant COMT inhibitor tolcapone (Apud et al., 2007). This provides a proof of principle that understanding the neural effects of a gene variant through a combined genetic imaging approach can contribute to the optimisation of therapy at an individual level. Importantly, the rs4680 variant also predicted prefrontal activation and working memory performance in response to therapy with olanzapine (Bertolino et al., 2004).

Fourth, to reiterate, the best animal model for psychiatric disorders is humans. Thus, a useful entry point for systems-level

neuroscience could be Phase 1 studies concomitant with the introduction of novel candidate medication. Here, neuroimaging can show how and to what degree relevant cerebral circuits are affected. The predictive value of this approach might be enhanced by stratifying healthy human subjects for common genetic risk factors (Section 4.2) Harrison, 2015; Kirov et al., 2013; Muglia, 2011; Doherty and Owen, 2014). In addition, certain facets of the psychopathology of schizophrenia can be transiently induced in humans. For example, psychotic episodes and cognitive dysfunction elicited by the psychotomimetic agent, ketamine, mimic the early phase of schizophrenia (D'Souza et al., 2012; Pomarol-Clotet et al., 2006). Neuroimaging of the influence of antipsychotics on the response to ketamine in the course of their early characterisation in humans could be instructive in preparing Phase II Proof of Concept studies. This strategy could be extended to the identification of well-defined "classifiers" that compare novel compounds as regards their systems-level effects to an array of previously-tested compounds.

Finally, systems-level data can be helpful in back-translation. By delineating neural systems properties that are consistently impacted in, for example, schizophrenia, then ascertaining which behaviours and circuits are under their control in rodents, new animal models might be designed. Their utility could be enhanced by mimicking genetic risk variants associated with the disorder (Section 4.3). Modelling CNVs could be especially fruitful in view of their high penetrance in schizophrenia and ASD-related disorders (Millan, 2013; Muglia, 2011; Nomura and Takumi, 2012; Doherty and Owen, 2014). An impressive example is a mouse model for the schizophrenia-associated microdeletion, 22q11 that shows abnormal hippocampal-prefrontal connectivity (Sigurdsson et al., 2010). Rodent neuroimaging, behavioural testing and neurochemistry (dialysis) will be essential for determining what corresponds in a rodent to human-specific symptoms of psychiatric disorders and their neurobiological substrates. This facet is helped by advances in rodent neuroimaging which can now delineate many of the same regions and circuits impacted in human psychiatric disorders (Gass et al., 2013; Gobert et al., 2011; Schwarz et al., 2013). Ultimately, this process of back-translation will be transformed into one of translation whereby studies are initially undertaken in experimental models with novel agents which are then taken into humans for neuroimaging of their systems-levels actions.

8.4. Lack of clinical efficacy in clinical trials: possible explanations and solutions

Where a drug "fails" in a clinical trial (usually, non-separation from placebo), the tendency is to consider the drug as inactive and/or its mechanism of action ineffective. Indeed, the major reason for drug discontinuation is almost invariably reported to be lack of efficacy (Pammolli et al., 2011). The assumption that the mechanism of action is irrelevant appears injudicious. In fact, the mechanism of action may simply be insufficient *alone* yet would be efficacious when associated with a complementary pharmacological activity, either in association or embedded in a multi-target agent (Section 7.1) (Millan, 2014a). Furthermore, it is important to consider some possible explanations of why a lack of efficacy may be more *apparent* than real and of several initiatives under way to improve trial sensitivity and avoid potential false negatives.

First, perhaps the best-known issue in trials of depression and schizophrenia is the increasing difficulty of separating drug from placebo which, in the context of a modern clinical trial, resembles a form of "psychotherapy" with multifarious neurobiological effects (Alphs et al., 2012; Enck et al., 2013; Melander et al., 2008; Benedetti, 2014). Ironically, this advantage will not usually be available in the real-world of treatment (Enck et al., 2013). Strategies for minimising the placebo response (which can be regionally variable in a multi-centric trial) include: greater patient homogeneity at recruitment; rigorous patient selection for disease/avoidance of borderline subjects; complementary clinician/patient readouts of efficacy; lead-in arms; and computer simulation of placebo dropouts. Since, they have been expertly discussed elsewhere, they do not need to be evoked in detail here (Alphs et al., 2012; De Bodinat et al., 2010; Enck et al., 2013; Gelenberg et al., 2008; Pilla Reddy et al., 2012). Nonetheless, it is worth briefly evoking one surprising and recently-identified factor detrimental to placebo-controlled trials, particularly in the US. That is, the participation of professional patients, who may even be enroled simultaneously in several trials. Duplicate patients are particularly astute in detecting whether they are on drug or placebo. Measures to exclude them from trials would improve the chances of statistically demonstrating that an active agent truly separates from placebo (Shiovitz et al., 2013). One initiative to this end is the web-based and New-Meds / IMI - sponsored "Dupcheck". Another issue concerning placebo is the performance of trials themselves since: (1), some patients will only join a trial under the precondition that they are not on placebo while (2), certain countries do not permit placebo-controlled trials, for example, for the long-term treatment of psychotic patients (Fleischhacker et al., 2002).

Second, when a compound is less active than expected, there may be a problem of target-engagement at the doses tested leading to a greater emphasis *via* PK/PD and biomarker studies *prior* to Proof of Concept investigations to ensure that the right dose range is evaluated (Gabrielsson et al., 2009; Gelenberg et al., 2008; Harmer et al., 2011; Scarr et al., in press) (Sections 2.7.2 and 8.2).

Third, improved compliance may greatly improve the reliability of clinical trials. Adherence can be actively favoured by strengthening the alliance of patients with clinicians and by implicating family and carers. In coming years, remote monitoring or patients may likewise enhance compliance and trial outcome (Garcia-Ribera and Bulbena, 2011; Leclerc et al., 2013; Olfson et al., 2014; Rabipour and Raz, 2012) (Section 8.7). The need to improve medication compliance is also critical to treatment outside the framework of clinical trials in daily clinical practise (Garcia-Ribera and Bulbena, 2011; Leclerc et al., 2013). In this regard, depot formulations are useful, for example for schizophrenia to reduce the risk of relapse (Altamura et al., 2012).

Fourth, another option to enhance the fidelity of clinical trials may be adaptive designs. This alludes to the use of information acquired from the trial itself (interim analyses) to adjust parameters without compromising trial integrity: one example concerns the use of surrogate markers that predict long-term drug efficacy soon after commencing administration (Bretz et al., 2009; Dragalin, 2011).

Fifth, conventional measures and rating scales may not be appropriate for novel mechanisms of action. The use of novel readouts may improve sensitivity to drug efficacy. Examples include emotional processing/cognitive bias in depression (Harmer et al., 2011) and new rating scales differentiating subdimensions of negative symptoms in schizophrenia (Foussias et al., 2014; Malaspina et al., 2014). In addition, measures of real-world function like hours worked or socially engaged would support claims for genuine clinical utility – and come closer to satisfying both the requirements of regulators and the needs of patients (Leifker et al., 2011; Rocca et al., 2014; Schennach et al., 2012). Patient reports in parallel to (but not instead of) carer and physician evaluation may also improve estimations of treatment efficacy and suggest novel therapeutic opportunities (Ishak et al., 2014). Not surprisingly, efforts are also being made to find surrogate biomarkers of drug efficacy. However, it is unclear whether any *single* readout will suffice, rather multimodal biomarkers may be required. Note, further, that no surrogate measure of efficacy is currently recognised by the EMA or FDA in the absence of a demonstrated effect on patient function (Scarr et al., in press).

Sixth as regards trial design, rather than large, multicentre and inter-regional trials, one might undertake initial Proof of Concept trials on drugs with well-defined mechanisms of action in smaller, more homogeneous, stratified populations possessing an appropriate phenotype and pathophysiology as defined by the use of specific biomarkers (Gelenberg et al., 2008). For example, certain genotypes like the above-mentioned COMT polymorphism (Apud et al., 2007; Bertolino et al., 2004; Buckholtz and Meyer-Lindenberg, 2010) modulate the response to specific drug classes. Measures under study for potential patient stratification, in addition to genetic profiling, include EEG parameters, neuroimaging, emotional processing and cognitive function (Harmer et al., 2011; Murphy and Mackay, 2010; Scarr et al., in press; Schwarz et al., 2011).

Seventh, rare diseases may likewise provide a useful entrance point for subsequent clinical studies in larger and more heterogeneous populations, since they should be more sensitive for validating a specific mechanism of action. This is an attractive option in view of successful support by both the EMA and FDA of orphan drug/rare disease development (Butlen-Ducuing et al., 2010). A well-established example is Down syndrome for Alzheimer's disease (Ness et al., 2012; Weksler et al., 2013). One may also cite the evaluation of metabotropic glutamate receptor 5 antagonists and GABAergic modulators in monogenic Fragile X, before their intended evaluation in idiopathic ASD (Cook et al., 2014; Lozano et al., 2014; Pop et al., 2014). A further possibility concerns neurodevelopmental syndromes provoked by rare CNVs that are associated with a very high risk of ASD and schizophrenia (Kirov et al., 2013; Millan, 2013; Doherty and Owen, 2014).

Eighth, for a drug expected to be effective only against certain symptoms or against a discrete pathology, as pointed out above, it might best be evaluated in a stratified and homogeneous population. Alternatively, since certain neurobiological anomalies and domains of dysfunction ignore diagnostic boundaries, one might argue for a clinical trial in a target population defined *independently* of the psychiatric disorder. However, whether and how a novel agent could be clinically evaluated in a trans-nosological population remains to be established (Butlen-Ducuing et al., 2010).

Finally, for a novel trial design or an agent with a new mechanism of action, existing guidelines may be absent or poorly-adapted. Hence, early discussions with regulators at the FDA and EMA are actively encouraged. This can lead to mutual agreement on procedures for optimising the chances of demonstrating, for example, the efficacy of a course-altering agent in schizophrenia (Fusar-Poli et al., 2013; Harmer et al., 2011; Sabbag et al., 2011).

8.5. Personalised and precision medicine; future prospects

While the term "translational" is omnipresent in the literature, "personalised medicine" is not far behind. It emerges from the tenet that, as a rule of thumb, 1 in 3 people respond well to medication, 1 in three respond partly, and 1 in 3 poorly or not at all (Schlaepfer et al., 2012). Quite apart from disparities in drug metabolism (Evers, 2009; Kirchheiner et al., 2004), this differential responsiveness reflects patient heterogeneity at the genetic/epigenetic and neurobiological level, as well as contrasting profiles of dysfunction (Cole et al., 2011; Hariri, 2009; Honey et al., 2008; Tansey et al., 2012; Uher, 2011). Interestingly, this phenomenon is not confined to pharmacotherapy, but is also apparent as regards the effects of, for example, Cognitive Behavioural Therapy for depression, where contrasting efficacy has been related to patient personality (Bagby et al., 2008). Clearly, then, there is often a mismatch between treatment and patient phenotype.

Currently, pharmacogenomic studies of Cytochrome genotype – which influences the metabolism of drugs like antidepressants and antipsychotics – are helpful in informing the choice of medication (Kirchheiner et al., 2004). In an extrapolation of the stratification of *subpopulations* for clinical studies, tailored (or personalised) medicine implies the more comprehensive genotyping and phenotyping of *individuals* as regards functional deficits and neurobiological abnormalities (Klöppel et al., 2012; Sams-Dodd, 2013; Scarr et al., in press; Tansey et al., 2012). In the case where a defined drug mechanism of action has been designed to correct a specific pathophysiological substrate, the term precision medicine has been coined: this is reminiscent of a key and lock relationship and, in a similar manner, may differ between patients (Insel, 2014). Precision medicine assumes that the medicine is available and that we are in position to identify exactly which patients would be responsive. It tends to ignore the complex and multi-factorial nature of psychiatric disorders, even for a *single* patient in terms of both symptoms and neurobiological anomalies – patients might need several classes of precision medicine to cover diverse pathologies and symptoms. Further, precision medicine would require biomarkers of very high fidelity and predictive value at the individual level.

The concepts of biomarker-enabled, tailored and precision medicine are crucial in focusing attention on the wish to better match medication to patient characteristics, rather than attempt blanket treatments which inevitably will fail some patients (Sams-Dodd, 2013; Scarr et al., in press; Tansey et al., 2012). While group means and statistical differences are paramount outcomes of clinical studies of large populations, the more proximate need of the practising physician and psychiatrist is the single person facing them, and the wish to choose the most appropriate therapy for that individual. It is important that

we are now moving towards that goal. However, on medical, ethical and economic grounds, the broad-based application of personalised and precision medicine is not currently realistic and remains a long-term aspiriation for the future (Davis et al., 2009; Evers, 2009; Guttmacher et al., 2010). For the time being, needs- and evidence-based medicine are more pragmatic and attainable goals.

8.6. Non-pharmacotherapeutic treatments, alone and in association with medication

As pointed out above, drugs act on proteins or on other molecules, not on cerebral circuits *per se*. Despite the potential merits of multi-target strategies in this regard (Section 7.1), it is interesting to consider non-pharmacotherapeutic strategies that intervene at the neural network level. Deep-brain stimulation of the subgenual cortex in the treatment of refractory depression, and transcranial stimulation (depression and schizophrenia) recruit clusters of neurones distributed *across* the frontal cortex (Block and Nemeroff, 2014; Du et al., 2012; Fox et al., 2012; Kalu et al., 2012; Martin and Martín-Sánchez, 2012; Patel et al., 2010; Schlaepfer and Bewernick, 2013; Schlaepfer et al., 2012). Nonetheless, these and related approaches are procedure-dependent, hard to standardise and their applicability and reproducibility are still under scrutiny, so they are unlikely at any time soon to assume a universal role in the control of psychiatric disorders (Block and Nemeroff, 2014; Holtzheimer et al., 2012; Martin and Martín-Sánchez, 2012).

Cognitive or "brain" training has been suggested to enhance the plasticity of neural circuits and synapses (May, 2011; Rabipour and Raz, 2012). Various modes of psychosocial-cognitivo-behavioural intervention and psychoeducation presumably also act at the circuit level. They include cognitive-behavioural therapy with possibly enduring effects in depression, as well as cognitive remediation and social skills therapy for improvement of cognitive and social performance in schizophrenia (Cuijpers et al., 2010; DeRubeis et al., 2008; Kurtz, 2012; Patel et al., 2010; Penn et al., 2007; Ritchey et al., 2011; Statucka and Walder, 2013; Warmerdam et al., 2010). There is good evidence that, under appropriate conditions, when performed by experts and in responsive patients, these strategies are effective: however, the amplitude and specificity of effect still needs further study in controlled trials (Lynch et al., 2010; Rabipour and Raz, 2012). Further, owing to the need for (1), skilled practitioners; (2), the labour- and time-intensive nature of psychotherapeutic interventions and (3), differences in outcome even between expert centres, the long-term efficacy, large-scale applicability and cost-effectiveness of psychotherapy warrant further clarification (Webb et al., 2013; Wiles et al., 2013).

In any event, non-pharmacotherapeutic approaches are clearly important, and specifically advocated by national organisations under some circumstances, like first-line treatment of subjects at high risk of conversion to schizophrenia (Fusar-Poli et al., 2013). Their judicious further study and association with medication both in practise – and, if feasible, in clinical trials – appears desirable (Browning et al., 2011; Hollon et al., 2014; Swerdlow, 2012; Wiles et al., 2013). An example of the combination of pharmacological and psychotherapeutic interventions is provided by studies of the NMDA receptor partial agonist, D-cycloserine, to hasten fear-conditioned extinction and the treatment of phobias (Smits et al., 2013). The treatment of social phobias or impaired social cognition might also be undertaken by associating appropriate psychotherapy with the pro-social neuropeptide oxytocin (Meyer-Lindenberg et al., 2011).

The specificity and effectiveness of other strategies like exercise and meditation, alone and together with medication, in the treatment and prevention of psychiatric disorders requires further clarification and more rigorous evaluation (Goyal et al., 2014; Van Praag, 2009).

8.7. Digital health: a rapidly expanding new domain of activity

As for all other domains of life, R&D into, and the treatment of, psychiatric disorders is not immune to invasion by the "e"-world. This is manifested in several different ways (Kaltenbach, 2014).

First, on-line patient consultation with a health professional by video of some other computerised interface, while informal patient self-help and self-diagnosis is already a reality "thanks" to innumerable internet sites (Daker-White and Rogers, 2013; Kaltenbach, 2014; Warmerdam et al., 2010).

Second, there are many studies of computerised therapy in use. These include social, cognitive, problem-solving video-games and psychoeducative training for subjects with depression, anxiety disorders or schizophrenia. In certain cases, patients are acting autonomously, yet in other instances, the therapy is family-based or undertaken with a physician (Daker-White and Rogers, 2013; Depp et al., 2014; Harrison et al., 2011a, 2011b; Rabipour and Raz, 2012; Rotondi et al., 2010; Sacks et al., 2013; Subramaniam et al., 2012; Vinogradov et al., 2012; Warmerdam et al., 2010). Reasons driving this explosive development (apart from the commercial, and the arrival of firms not traditionally committed to mental health) are manifold. Some patients may prefer to avoid consultation, while others would like to take a more pro-active role in their own therapy. As regards health services, at-home electronic solutions and portable devices avoid the need for patients to travel to distant treatment centres, therapy provided over the Internet short-circuits the problem of limited staff/expertise for treating patients, and it is low-cost (Kaltenbach, 2014; Rotondi et al., 2010). Reports have usually been positive (above citations) as regards benefits. However, rigorous and controlled data on efficacy, specificity, risks and long-term consequences remain meagre so much further study is warranted.

Third, another notion that is emerging is that of electroceuticals whereby, mirroring the use of electronic chips in prosthetics, nanotechnology-engineered implants might be used to modulate the activity of neural circuits in the brain (Skripka-Serry, 2013).

Fourth, smart technologies (like Phone APPs) are being developed to share data and to advise, inform and remotely monitor patients, including their location, locomotor activity and glucose status etc. This may help adherence by alerting physicians to abnormalities (Depp et al., 2014; Granholm et al., 2012; Harrison et al., 2011a, 2011b). For example, if a bipolar

patient becomes hyperactive and/or desynchronised, this information would be transmitted to the clinician who could contact the patient or send e-guidance leading to resynchronisation. The EU has launched a major IMI initiative on remote monitoring entitled "RADAR".

Finally, a scannable barcode encoding pharmacogenomic information (like Cytochrome profile) can be carried by patients (and healthy subjects) for rapid physician consultation in the event that they require treatment with psychotropic or other classes of agent (Samwald and Adlassnig, 2013).

Strategies for digital health will ineluctably expand and will not necessarily be driven purely by medical considerations, so it is important to kept track of events and attempt to influence their evolution in an objective and positive manner benefitting patients.

9. Changes in the infrastructure and organisation of R&D (Table 4)

9.1. Altered roles of academia and industry and their interaction

In recent years the landscape of R&D for drug discovery has profoundly changed as regards both Industry and Academia, and also as regards the way in which they interact with each other.

A well-publicised concern has been the relative withdrawal of Big Pharma from R&D in the domain of psychiatric disorders and the down-sizing of internal capacities in favour of a business model driven more by outsourcing of studies on new medication targets and drug candidates, and the licensing-in of innovative new compounds at various stages from discovery leads to Phase III (Hunter, 2014; Khanna, 2012; Pammolli et al., 2011). As part of this strategy, complex, specialised and time-consuming technologies needed for work on novel targets (and not available in house) would be sought externally. Conversely, well-established core activities and areas of particular expertise would be strengthened in-house in order to facilitate effective collaboration with outside groups, attract new partners and to undertake important studies not possible elsewhere. It is also important that internal flexibility and reactivity are not compromised since it is wise to run several contrasting projects simultaneously, and also since priorities can rapidly change for a variety of reasons. Not surprisingly, the brunt of safety studies, late-phase clinical development and registration would be done by Pharma. Finally, the more precocious and pro-active influence of commercial reflections in the R&D process should be noted. There is clearly a need to integrate longer-term budgetary factors into early-phase project planning, but it should be undertaken carefully since its impact upon innovation will not necessarily be favourable (Applbaum, 2009).

On the other side of the fence, scarcer public funding, internal pressure to attract investment and greater public scrutiny of the relevance of research has prompted marked changes in academic labs. High-profile publications and a solid standard of teaching remain primordial but are being coupled to: more intense efforts to attract financial support; fee for data type services; greater attention (underpinned by university lawyers) to the commercial valorisation of discoveries through patents and their licencing and new modes of collaboration with Industry (Hunter, 2014; Khanna, 2012; Larivière et al., 2013; Ségalat, 2010). In essence, academic centres are increasingly positioning themselves in the same arena as biotech firms by aiming to generate new concepts and compounds for clinical development, and in devising new strategies for drug characterisation. Academic groups have, in fact, become increasingly skilled in working towards well-established endpoints in a defined timescale as usually required by industrial collaborations compared with the looser framework of public funding. In parallel, with the aid of industry refugees, and exploiting both medicinal chemistry and chemical libraries in the public domain, numerous Universities have set up units devoted to drug discovery (Comley, 2013; 2014; Hayden, 2014; Hunter, 2014; Khanna, 2012; Schultz-Kirkegaard and Valentin, 2014; Slusher et al., 2013). One encouraging aspect is that, for medicine in general, small and medium-sized biotech companies, to which such university units would effectively correspond, have been significant contributors to novel compounds over recent years (Barden and Weaver, 2010; Di Masi and Grabowski, 2007; Schultz-Kirkegaard and Valentin, 2014). Finally, there have even been initiatives to undertake (so far-mitigated success) early clinical trials. This is illustrated by "TURNS" programme for improving cognition in schizophrenia (NIH), while the above-mentioned National Centre for Translational Research is mainly focused on new agents providing insights not only into efficacy but also into the pathophysiological underpinnings of psychiatric disorders (Insel, 2014; Marcou et al., 2009; Reardon, 2014).

More recently, the nature of exchange and cooperation has been ramped up with moves to data-sharing and Open Innovation. For example, firms may offer their own chemical libraries to academia, access to phenotype screens or even lab space to perform promising projects (Hunter 2014; Khanna, 2012; Kneller et al., 2014; Lee et al., 2011; Woodcock, 2010). The firm in question would in principle have the right of first refusal for major discoveries though, depending on the nature of the agreement, Industry and/or Academia would usually enjoy Intellectual Property rights. Indeed, there are a number of variations around this core idea, but the basic idea is the perceived need by Pharma to enrich the pipeline by also looking elsewhere for novel ideas and compounds.

In any event, the centre of gravity for primary drug discovery has somewhat shifted, and new skill sets will be needed both in Industry and in Academia. The jury is still out on all this but, while regretting the lesser emphasis on CNS R&D and genuine research in Industry itself, it is hoped that these changes will indeed generate more diversity, productivity and efficiency in the search for new therapeutic targets and hence revitalise therapeutic progress for psychiatric disorders and other diseases (Hayden, 2014; Hunter, 2014; Olesen et al., 2006; Schultz-Kirkegaard and Valentin, 2014; Schumann et al., 2014).

9.2. Pre-competitive collaborations involving multiple partners

While the above comments focused on the changing roles of industry and academia and their relationship, an especially

important development over the last 10 years has been the broader coming-together of major stakeholders including regulators and patients (Section 9.5) (Eichler et al., 2013; Goldman, 2012; Khanna, 2012). This process has been promoted and financed by national institutions like the NIH and supranational bodies like the EU, in the latter case *via* the heavily-funded IMI collaboration. This, as the name implies, is a response to the perceived penury of new drugs for psychiatric disorders – and other domains – and an attempt to revitalise drug discovery and development (Goldman, 2012; Khanna, 2012; Van der Feltz-Cornelis et al., 2014; Woodcock, 2010). A diversity of consortia coalesce multiple academic groups and industrial partners into a pre-competitive environment to collectively search for solutions to problems like: data reproducibility and sharing; the need for better translational tools for drug characterisation in depression and schizophrenia (NewMeds); and/or enhancing our understanding of the causes of autism ("EU-AIMS") (Woodcock, 2010). Another illustration of the path taken by IMI to promote drug discovery in the EU is its setting up a European Lead Centre, again a joint academic and industrial venture (Comley, 2014; Hunter, 2014).

9.3. A global vision of R&D for improving the treatment of psychiatric disorders

From the above comments, it is apparent that the commitment to improve treatment of psychiatric disorders transgresses national frontiers. Along these lines, there have been many important and welcome moves to extend progress in neuropsychopharmacology to economically less-favoured regions and to establish a genuinely global framework for researching and improving brain health (Abbott and Schiermeier, 2014; Beddington et al., 2008; Cameron et al., 2009; Di Luca et al., 2011; Downs and Blackburn, 2012; Haro et al., 2014; Khanna, 2012; Larivière et al., 2013; Olesen et al., 2006; Schumann et al., 2014). It should not, however, be forgotten that in many regions success will depend upon a broader sweep of strategies for improving basic health care, living standards and hygiene, for countering isolation and poverty, and for promoting greener urbanism and environmental protection (Alcock et al., 2014; Astell-Burt et al., 2013; Collins et al., 2013; Murray et al., 2010; Nutsford et al., 2013; Ochodo et al., 2014; Richardson et al., 2013; Sharan et al., 2009; Tomlinson et al., 2009). The single greatest future threat to mental (and physical) health is arguably the local degradation of the environment and ecosystems exacerbated by climate warning (McClanahan et al., 2012; Millan, 2006; Roff and Mumby, 2012). Without resolving this issue, it is to be feared that much of what is discussed herein will, for many people, be of only peripheral importance.

At another level, the cultural, genetic and other differences between continents and countries are being better recognised with, for example, specific patterns of development and use of drugs in Asian *vs* Western counties.

9.4. Big data: production, storage, sharing and analysis

The multi-group collaborations evoked above; world-wide initiatives for mental health; open reporting of experimental and clinical studies; astronomical volumes of data cascading from genome-sequencing and gene-association studies; brain-mapping projects like the Human Brain Project; longitudinal studies on large cohorts of patients; and multiplexed HTS assays exemplify the increasingly massive quantities of data being generated, stored, analysed and shared in the pursuit of R&D to improve brain health (Alivisatos et al., 2012; Buck, 2014; Deco and Kringelbach, 2014; Kaltenbach, 2014; Lee et al., 2011; Skripka-Serry, 2013). The term "Big Data" refers to the challenges faced in handling and analysing gigantic volumes of information both within and between institutions, and for which new tools and increased computing power are being developed (Buck, 2014; Williams and Denny-Gouldson, 2013). One interesting strategy is web-co-ordinated crowd-sourcing of gamers (Khatib et al., 2011). Data warehouses will also be an important asset in this endeavour, though questions of confidentiality, ownership and protection are issues awaiting clearer resolution. One example of innovation for big data management is eTricks (Delivering European Translational Information and Knowledge Management Services), a system derived from one originally developed by Janssen, that is used to share data within the framework of IMI collaborations.

Though information technology will presumably evolve to cope with the barrage of data, a less tractable problem will be the ability of humans to assimilate, understand and intelligently act on the information generated. A simple example is provided by the proverbial (and now literal) thousand Dollar genome which individuals can purchase, yet which neither they nor anyone else can precisely interpret and act on to their benefit (Goldman and Domschke, 2014).

9.5. The increasing implication of patients in the R&D process

Rather than having themselves sequenced, there are other more tangible and important ways in which individuals, including patients and their carers can contribute to progress for brain health. It is, thus appropriate to conclude this article in emphasizing that the role of patients themselves has significantly evolved over the years as regards the search for improved control of their disorders (Richards et al., 2013).

For many years, patients were mainly passive actors receiving treatment and taking part in clinical trials. However, patients and their families have all been, at least to some extent, empowered by the availability of information from the Internet which has subtly modified their status and relationship to health professionals. They now have more awareness and understanding of the nature and significance of psychiatric disorders and their management (Jorm, 2012; Coles and Coleman, 2010; Richards et al., 2013)

As pointed out above, within the context of clinical trials, patient reports are accepted as important counterparts to physician assessments. In clinical practise, patient motivation and alliances with therapists are better and reciprocally understood to be important element for compliance and therapeutic success (Section 8.4). As represented by online communities and Patient Associations, there is much greater involvement of patients and their carers in the process of R&D for psychiatric disorders. They are recognised as equal partners by other parties

from industry to regulators to academia. For example, Associations are important partners in certain consortia mentioned above, participate in ECNP-organised meetings on CNS disorders (Nutt and Goodwin, 2011), and they are invited to EMA workshops on treatment guidelines. In addition, the European Brain Council incorporates patient groups that advise the Commission in Brussels as concerns its strategies for enhancing mental health. By these channels of communication, and input to medical journals patients can provide crucial information on their daily lives, outstanding therapeutic needs, medication preferences, criteria for diagnosis, trials design and their propensity to accept risks in an effort to find better treatments (Eichler et al., 2013; Johnson et al., 2009; Kocsis et al., 2009; Richards et al., 2013).

Globally speaking then, though not without risks, patients are increasingly integrated in various ways in the quest to improve the knowledge and treatment of those psychiatric disorders from which they themselves suffer.

Finally, it should not be forgotten that private donations to Patient Charities have traditionally been a core source of funding in for example the UK, and with pressure on finance for R&D, this contribution is even more important than before (Downs and Blackburn, 2012).

10. Concluding comments

From the above text as well as the Tables and Figures, it may be seen that neuropsychopharmacology, neuropsychiatry and neuroscience in general have come a very long way since the advent of the first psychotropic agents in the 1950s. Further, these fields are currently in a state of transition whereby, as discussed herein, we need to "learn from the past and look to the future" in moving forward. The above paragraphs encapsulate a remarkably large number and diversity of shifts in thinking (and actual ways of performing R&D) that have emerged over the last few years, and things will continue to evolve over the coming decades. However, the most fundamental issue of all, how to improve the prevention and treatment of people suffering from – or at risk of – psychiatric disorders is the most challenging and lengthy to resolve, not least in view of the frustratingly high time-constants. Moving from an idea to its pharmaco-therapeutic concretisation in patients can take in the order of 20–25 years. Indeed, *time* is a key word here. Sequencing the human genome was a seminal and game-changing event but certainly did not trigger a rapid paradigm-shift from a *therapeutic* perspective. While, in the long-term, it will be a resource of decisive importance, it initially led to naïve exceptions that all was soon going to be swiftly resolved, and hence unwittingly detracted from other ongoing and promising projects by diverting increasingly scarce resources into genomics, genetics and related disciplines. We how recognise not only the power but also the limits of this cottage industry, and studies of the human genome in general. Moreover, it is critical to realise that much time will still be needed before we fully understand the intertwined causes of psychiatric disorders and can propose improved pharmacotherapeutic and other strategies for their control. In this regard too, it is hard not to evoke a second core element of *money*. It is imperative that this period of transition for the R&D of CNS disorders is adequately, fairly and durably funded. This includes the public and private provision of permanent jobs for engaged, gifted and skilled young collaborators indispensable for future success. Thus, both time (patience, perseverance and commitment) and money (wisely spent on human and material resources) will be necessary to systematically generate a third core element of success, *knowledge*, in the search for improved understanding and control of psychiatric disorders and other diseases of the brain.

Finally, the domains of progress and ideas outlined in the present paper encourage rekindled optimism that the more effective treatment – and eventually prevention – of debilitating psychiatric disorders (and other diseases of the brain) will sooner rather than later be within our reach. However, this will require a sustained commitment by all the major partners concerned by this venture, from industry to academia, clinicians to patients, regulators to public policy makers and, indeed, from society at large.

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Contributors

MJM prepared the tables and wrote a first draft of the paper with the exception of the Historical Section (mainly prepared by SO, but also MJM), of the discussion of DSM-5 and "normality" (GG and MJM) and Translational Neuroimaging (AML). All authors read, contributed to, improved and approved this final version of the paper.

Conflict of interest

Mark J. Millan is a full time employee of the Institut de Recherche Servier and has no other interests to declare. In the last 3 years, Guy Goodwin has held grants from Servier and received honoraria for speaking or chairing educational meeting from Abbvie, AstraZeneca, GSK, Lundbeck, Medscape, Servier and advised AstraZeneca, Cephalon/Teva, Lundbeck, Merck, Otsuka, P1Vital, Servier, Shire, Sunovion, and Takeda. He holds shares in P1vital and acted as expert witness for Lilly. In the last three years, Andreas Meyer-Lindenberg has received honoraria for speaking and for educational activities from Abbott GmbH & Co. KG, BASF SE, Servier Deutschland GmbH, Outcome Europe Sárl, H. Lundbeck A/S, Lilly Deutschland GmbH, Hoffmann-La Roche Ltd., Astra Zeneca GmbH, Groupo Ferrer Int., and Janssen-Cilag GmbH. Sven Ogren is a senior Professor at the Karolinska Institute and has no other interests to declare. All Officers are or were (SO) members of the ECNP Executive Committee. The opinions and ideas expressed in this article do not necessarily represent those of either the Author's primary employers, nor of the ECNP.

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References

Aan Het Rot, M., Zarate, C.A., Charney, D.S., Mathew, S.J., 2012. Ketamine for depression: where do we go from here? Biol. Psychiatry 72, 537–547.

Abbas, A.I., Hedlund, P.B., Huang, X.P., Tran, T.B., Meltzer, H.Y., Roth, B.L., 2009. Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology 205, 119–128.

Abbott, A., Schiermeier, Q., 2014. After the Berlin Wall: Central Europe up close. Nature 515, 22–25.

Alcock, I., White, M.P., Wheeler, B.W., Fleming, L.E., Depledge, M.H., 2014. Longitudinal effects on mental health of moving to greener and less green urban areas. Environ. Sci. Technol. 48, 1247–1255.

Al-Hamzawi, A.O., Gureje, O., Huang, Y., Hu, C., Bromet, E.J., Viana, M.C., Hinkov, H.R., Karam, E.G., Borges, G., Florescu, S.E., Williams, D.R., Demyttenaere, K., Kovess-Masfety, V., Matschinger, H., Levinson, D., De Girolamo, G., Ono, Y., de Graaf, R., Oakley, Browne, M., Bunting, B., Xavier, M., Haro, J.M., Kessler, R.C., 2015. Proportion of patients without mental disorders being treated in mental health services worldwide. Br. J. Psychiatry 206, 101–109.

Alivisatos, A.P., Chun, M., Church, G.M., Greenspan, R.J., Roukes, M.L., Yuste, R., 2012. The brain activity map project and the challenge of functional connectomics. Neuron 74, 970–974.

Allgulander, C., Baldwin, D.S., 2013. Pharmacotherapy of generalized anxiety disorder. Mod. Trends Pharmacopsychiatr. 29, 119–127.

Alphs, L., Benedetti, F., Fleischhacker, W.W., Kane, J.M., 2012. Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it? Int. J. Neuropsychopharmacol. 15, 1003–1014.

Altamura, A.C., Aguglia, E., Bassi, M., Bogetto, F., Cappellari, L., De Giorgi, S., Fagiolini, A., Ferrannini, L., Girardi, P., 2012. Rethinking the role of long-acting atypical antipsychotics in the community setting. Int. Clin. Psychopharmacol. 27, 336–349.

Alvarez, E., Perez, V., Artigas, F., 2014. Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder. Neuropsychiatr. Dis. Treat. 15, 1297–1307.

Anthony, K.R., Marshall, P.A., Abdulla, A., Beeden, R., Bergh, C., Black, R., Eakin, C.M., Game, E.T., Gooch, M., Graham, N.A., Green, A., Heron, S.F., van Hooidonk, R., Knowland, C., Mangubhai, S., Marshall, N., Maynard, J.A., McGinnity, P., McLeod, E., Mumby, P.J., Nyström, M., Obura, D., Oliver, J., Possingham, H.P., Pressey, R.L., Rowlands, G.P., Tamelander, J., Wachenfeld, D., Wear, S., 2015. Operationalizing resilience for adaptive coral reef management under global environmental change. Glob. Change Biol. 21, 48–61.

Applbaum, K., 2009. Is marketing the enemy of pharmaceutical innovation? Hastings Cent Rep 39, 13–17.

Apud, J.A., Mattay, V., Chen, J., Kolachana, B.S., Callicott, J.H., Rasetti, R., Weinberger, D.R., 2007. Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology 32, 1011–1020.

Arana, G.W., 2000. An overview of side effects caused by typical antipsychotics. J. Clin. Psychiatry 61, 5–11.

Arango, A., 2015. Present and future of developmental Neuropsychopharmacology. Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2014.11.003.

Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H., Robitaille, R., Volterra, A., 2014. Gliotransmitters travel in time and space. Neuron 81, 728–739.

Arey, R.N., Enwright, J.F., 3rd, Spencer, S.M., Falcon, E., Ozburn, A.R., Ghose, S., Tamminga, C., McClung, C.A., 2014. An important role for cholecystokinin, a CLOCK target gene, in the development and treatment of manic-like behaviors. Mol. Psychiatry. 19, 342–350.

Arnone, D., McKie, S., Elliott, R., Juhasz, G., Thomas, E.J., Downey, D., Williams, S., Deakin, J.F., Anderson, I.M., 2013. State-dependent changes in hippocampal grey matter in depression. Mol. Psychiatry 18, 1265–1272.

Arnsten, A.F., 2006. Stimulants: therapeutic actions in ADHD. Neuropsychopharmacology 31, 2376–2383.

Arnsten, A.F., Steere, J.C., Hunt, R.D., 1996. The contribution of alpha2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry 53, 448–455.

Artigas, F., 2015. Developments in the field of antidepressants, where do we go now? Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2013.04.013.

Artigas, F., 2013. Serotonin receptors involved in antidepressant effects. Pharmacol. Ther. 137, 119–131.

Astell-Burt, T., Feng, X., Kolt, G.S., 2013. Mental health benefits of neighbourhood green space are stronger among physically active adults in middle-to-older age: evidence from 260,061 Australians. Prev. Med. 57, 601–606.

Aston-Jones, G., Deisseroth, K., 2013. Recent advances in optogenetics and pharmacogenetics. Brain Res. 1511, 1–5.

Atack, J.R., Wafford, K.A., Street, L.J., Dawson, G.R., Tye, S., Van Laere, K., Bormans, G., Sanabria-Bohórquez, S.M., De Lepeleire, I., de Hoon, J.N., Van Hecken, A., Burns, H.D., McKernan, R.M., Murphy, M.G., Hargreaves, R.J., 2011. MRK-409 (MK-0343), a GABAA receptor subtype-selective partial agonist, is a non-sedating anxiolytic in preclinical species but causes sedation in humans. J. Psychopharmacol. 25, 314–328.

Axelrod, J., Whitby, L.G., Hertting, G., 1961. Effect of psychotropic drugs on the uptake of H3-norepinephrine by tissues. Science 133, 383–384.

Ayd, F.J., 1963. Chlorpromazine: ten years' experience. J. Am. Med. Assoc. 184, 51–54.

Baell, J., Walters, M.A., 2014. Chemistry: chemical con artists foil drug discovery. Nature 513, 481–483.

Bagby, R.M., Quilty, L.C., Segal, Z.V., McBride, C.C., Kennedy, S.H., Costa, P.T., 2008. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. Can. J. Psychiatry 53, 361–370.

Baldomero, E.B., Ubago, J.G., Cercos, C.L., Ruilova, J.V., Calvo, C.G., Lopez, R.P., 2005. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. Depress. Anxiety 22, 68–76.

Baldwin, D.S., Ajel, K., 2007. Role of pregabalin in the treatment of generalized anxiety disorder. Neuropsychiatr. Dis. Treat. 3, 185–191.

Baldwin, D.S., Ajel, K., Masdrakis, V.G., Nowak, M., Rafiq, R., 2013. Pregabalin for the treatment of generalized anxiety disorder: an update. Neuropsychiatr. Dis. Treat. 9, 883–992.

Ballard, E.D., Ionescu, D.F., Vande Voort, J.L., Niciu, M.J., Richards, E.M., Luckenbaugh, D.A., Brutsché, N.E., Ameli, R., Furey, M.L., Zarate, C.A., 2014. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J. Psychiatr. Res. 58, 161–166.

Ban, T.A., 1969. Psychopharmacology Baltmore. Williams & Wilkins.

Ballon, J., Stroup, T.S., 2013. Polypharmacy for schizophrenia. Curr. Opin. Psychiatry 26, 208–213.

Bang-Andersen, B., Ruhland, T., Jørgensen, M., Smith, G., Frederiksen, K., Jensen, K.G., Zhong, H., Möller Nielsen, S., Hogg, S., Mörk, A., Stensböl, T.B., 2011. Discovery of 1-[2-(2,4-dimethylphenyl-sulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J. Med.Chem. 54, 3206–3221.

Barden, C.J., Weaver, D.F., 2010. The rise of micropharma. Drug Discov. Today 15, 84–87.

Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol. Bull. 121, 65–94.
Barkley, R.A., 2006. Attention-deficit Hyperactivity Disorder. A Handbook for Diagnosis and Treatment. Guilford, New York, 258.
Bartzokis, G., 2012. Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. Neuropharmacology 62, 2137–2153.
Basnasr, M., Chowdhury, G.M., Terwilliger, R., Newton, S.S., Duman, R.S., Behar, K.L., Sanacora, G., 2010. Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. Mol. Psychiatry 15, 501–511.
Beddington, J., Cooper, C.L., Field, J., Goswami, U., Huppert, F.A., Jenkins, R., Jones, H.S., Kirkwood, T.B.L., Sahakian, B.J., Thomas, S.M., 2008. The mental wealth of nations. Nature 455, 1057–1060.
Benedetti, F., 2014. Placebo effects: from the neurobiological paradigm to translational implications. Neuron 84, 623–637.
Benitez-King, G., Riquelme, A., Ortiz-Lopez, L., Berlanga, C., Rodriguez-Verdugo, 2011. A non-invasive method to isolate the neuronal linage from the nasal epithelium from schizophrenic and bipolar diseases. J. Neurosci. Methods 201, 35–45.
Bernstein, H.G., Steiner, J., Guest, P.C., Dobrowolny, H., Bogerts, B., 2015. Glial cells as key players in schizophrenia pathology: recent insights and concepts of therapy. Schizophr. Res. 161, 4–18.
Berridge, C.W., Arnsten, A.F., 2013. Psychostimulants and motivated behavior: arousal and cognition. Neurosci. Biobehav. Rev. 37, 1976–1984.
Berridge, M.J., Downes, C.P., Hanley, M.R., 1982. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem. J. 206, 587–595.
Bertolino, A., Caforio, G., Blasi, G., De Candia, M., Latorre, V., Petruzzella, V., Nardini, M., 2004. Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am. J. Psychiatry 161, 1798–1805.
Bidwell, L.C., Dew, R.E., Kollins, S.H., 2010. Alpha2 adrenergic receptors and attention-deficit/hyperactivity disorder. Curr. Psychiatry Rep. 12, 366–373.
Blackburn, K.J., French, P.C., Merrills, R.J., 1967. 5-hydroxytryptamine uptake by rat brain in vitro. Life Sci. 6, 1653–1663.
Blazer, L.L., Neubig, R.R., 2009. Small molecule protein-protein interaction inhibitors as CNS therapeutic agents: current progress and future hurdles. Neuropsychopharmacol. Rev. 34, 126–141.
Block, S.G., Nemeroff, C.B., 2014. Emerging antidepressants to treat major depressive disorder. Asian J. Psychiatry 112, 7–16.
Blumstein, D.T., Ebensperger, L.A., Hayes, L.D., Vásquez, R.A., Ahern, T.H., Burger, J.R., Dolezal, A.G., Dosmann, A., González-Mariscal, G., Harris, B.N., Herrera, E.A., Lacey, E.A., Mateo, J., McGraw, L.A., Olazábal, D., Ramenofsky, M., Rubenstein, D.R., Sakhai, S.A., Saltzman, W., Sainz-Borgo, C., Soto-Gamboa, M., Stewart, M.L., Wey, T.W., Wingfield, J.C., Young, L.J., 2010. Toward an integrative understanding of social behavior: new models and new opportunities. Front. Behav. Neurosci. 4, 34.
Bolding, M.S., White, D.M., Hadley, J.A., Weiler, M., Holcomb, H.H., Lahti, A.C., 2012. Antipsychotic drugs alter functional connectivity between the medial frontal cortex, hippocampus, and nucleus accumbens as measured by H215O PET. Front. Psychiatry 6, 105.
Borsook, D., Hargreaves, R., Becerra, L., 2011. Can functional magnetic resonance imaging improve success rates in CNS drug discovery? Expert Opin. Drug Discov. 6, 597–617.
Boulenger, J.P., Loft, H., Olsen, C.K., 2014. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study to the acute treatment of adult patients with major depressive disorder. Int. Clin. Psychopharmacol. 29, 138–149.
Bottegoni, G., Favia, A.D., Recanatini, M., Cavalli, A., 2011. The role of fragment-based and computational methods in polypharmacology. Drug Discov. Today 17, 23–34.
Bradley, C., 1937. The behavior of children receiving benzedrine. Am. J. Psychiatry 94, 577–585.
Bradley, S.R., Uslaner, J.M., Flick, R.B., Lee, A., Groover, K.M., Hutson, P.H., 2012. The mGluR7 allosteric agonist AMN082 produces antidepressant-like effects by modulating glutamatergic signaling. Pharmacol. Biochem. Behav. 101, 35–40.
Bray, N.J., Kapur, S., Price, J., 2012. Investigating schizophrenia in a "dish": possibilities, potential and limitations. World Psychiatry 11, 153–155.
Brent, B.K., Thermenos, H.W., Keshavan, M.S., Seidman, L.J., 2013. Gray matter alterations in schizophrenia high-risk youth and early-onset schizophrenia: a review of structural MRI findings. Child Adolesc. Clin. N. Am. 22, 689–714.
Bretz, F., Branson, M., Burman, C.F., Chuang-Stein, C., Coffey, C.S., 2009. Adaptivity in drug discovery and development. Drug Develop. Res. 70, 169–190.
Broich, K., 2009. Committee for Medicinal Products for Human Use (CHMP) assessment on efficacy of antidepressants. Committee for Medicinal Products for Human Use. Eur. Neuropsychopharmacol. 19, 305–308.
Brown, A.S., Derkits, E.J., 2010. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am. J. Psychiatry, 167261–167280.
Brown, C., Schulberg, H.C., Madonia, M.J., Shear, M.K., Houck, P.R., 1996. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am. J. Psychiatry 153, 1293–1300.
Browning, M., Grol, M., Ly, V., Goodwin, G.M., Holmes, E.A., Harmer, C.J., 2011. Using an experimental medicine model to explore combination effects of pharmacological and cognitive interventions for depression and anxiety. Neuropsychopharmacology 36, 2689–2697.
Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J.S., 2009. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci. Biobehav. Rev. 33, 279–293.
Brüne, M., Brüne-Cohrs, U., 2006. Theory of mind evolution, ontogeny, brain mechanisms and psychopathology. Neurosci. Biobehav. Rev. 30, 437–455.
Buchanan, K.L., Grindstaff, J.L., Pravosudov, V.V., 2013. Condition dependence, developmental plasticity, and cognition: implications for ecology and evolution. Trends Ecol. Evol. 28, 290–296.
Buck, F., 2014. How digital innovation and collaboration is driving a global demand for effective reporting in research funding. Drug Discov. World (Spring), 70–76.
Buckholtz, J.W., Meyer-Lindenberg, A., 2012. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. Neuron 74, 990–1004.
Buist-Bouwman, M.A., de Graaf, R., Vellebergh, W.A.M., Ormel, J., 2005. Comorbidity of physical and mental disorders and the effect on work-loss days. Acta Psychiatr. Scand. 111, 436–443.
Burns, J.K., 2006. Psychosis: a costly by-product of social brain evolution in *Homo sapiens*. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 30, 797–814.
Butlen-Ducuing, F., Haas, M., Pani, L., van Zwieten-Boot, B., Broich, K., 2012. DSM-5 and clinical trials in psychiatry: challenges to come? Nat. Rev. Drug Discov. 11, 583–584.
Butlen-Ducuing, F., Rivière, F., Aarum, S., Llinares-Garcia, J., 2010. European medicines agency support mechanisms fostering orphan drug development. Drug News Perspect. 23, 71–81.
Bymaster, F.P., Calligaro, D.O., Falcone, J.F., Marsh, R.D., Moore, N.A., Tye, N.C., Seeman, P., Wong, D.T., 1996. Radioreceptor

binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14, 87–96.
Cade, J.F.J., 1949. Lithium salts in the treatment of psychotic excitement. Med. J. Aust. 36, 349–352.
Calabrese, J.R., Bowden, C.L., Sachs, G.S., Ascher, J.A., Monaghan, E., Rudd, G.D., 1999. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J. Clin. Psychiatry 60, 79–88.
Cameron, A., Ewen, M., Ross-Degnan, D., Ball, D., Laing, R., 2009. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet 373, 240–249.
Cameron, I.M., Reid, I.C., MacGillivray, S.A., 2014. Efficacy and tolerability of antidepressants for sub-threshold depression and for mild major depressive disorder. J. Affect. Disord. 166, 48–58.
Cannon, T.D., Chung, Y., He, G., Sun, D., Jacobson, A., van Erp, T.G., McEwen, S., Addington, J., Bearden, C.E., Cadenhead, K., Cornblatt, B., Mathalon, D.H., McGlashan, T., Perkins, D., Jeffries, C., Seidman, L.J., Tsuang, M., Walker, E., Woods, S.W., Heinssen, R., North American Prodrome Longitudinal Study Consortium, 2015. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol. Psychiatry 77, 145–157.
Cardinali, D.P., Srinivasan, V., Brzezinski, A., Brown, G.M., 2012. Melatonin and its analogs in insomnia and depression. J. Pineal Res. 52, 365–375.
Carlini, V.P., Machado, D.G., Buteler, F., Ghersi, M., Ponzio, M.F., Martini, A.C., Schioth, H.B., de Cuneo, M.F., Rodrigues, A.L., de Barioglio, S.R., 2012. Acute ghrelin administration reverses depressive-like behavior induced by bilateral olfactory bulbectomy in mice. Peptides 35, 160–165.
Carlsson, A., Corrodi, H., Fuxe, K., Hökfelt, T., 1969. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-alpha-ethyl-metatyramine. Eur. J. Pharmacol. 5, 357–366.
Carlsson, A., Lindqvist, M., Waldeck, B., 1958. On the presence of 3-hydroxytyramine in brain. Science 127, 471.
Carlsson, A., Lindqvist, M., 1963. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse. Brain Acta Pharmacol. Toxicol. 20, 140–144.
Carpenter, W.T., Koenig, J.I., 2008. The evolution of drug development in schizophrenia: past issues and future opportunities. Neuropsychopharmacology 33, 2061–2079.
Carroll, D., 2013. Gene editing re-writing genomes with targetable nucleases. Drug Discov. World (Fall), 47–54.
Carroll, F.I., Blough, B.E., Mascarella, S.W., Navarro, H.A., Lukas, R.J., Damaj, M.I., 2014. Bupropion and bupropion analogs as treatments for CNS disorders. Adv. Pharmacol. 69, 177–216.
Casey, B.J., Craddock, N., Cuthbert, B.N., Hyman, S.E., Lee, F.S., Ressler, K.J., 2013. DSM-5 and RDoC: progress in psychiatry research? Nat. Rev. Neurosci. 14, 810–814.
Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HT gene. Science 301, 386–389.
Castells, X., Ramos-Quiroga, J.A., Bosch, R., Nogueira, M., Casas, M., 2011. Amphetamines for attention deficit hyperactivity disorder in adults. Cochrane Database Syst Rev. Jun 15 (6), CD007813. http://dx.doi.org/10.1002/14651858.CD007813.pub2.
Castro, J.E., Diessier, S., Varea, E., Marquez, C., Larsen, M.H., Cordero, M.I., Sandi, C., 2012. Personality traits in rats predict vulnerability and resilience to developing stress-induced depression-like behaviors, HPA axis hyper-reactivity and brain changes in pERK1/2 activity. Psychoneuroendocrinology 37, 1209–1223.
Catafau, A.M., Bullich, S., 2013. Molecular imaging PET and SPECT approaches for improving productivity of antipsychotic drug discovery and development. Curr. Med. Chem. 20, 378–388.
Cavalla, D., 2009. APT drug R&D: the right active ingredient in the right presentation for the right therapeutic use. Nat. Rev. Drug Discov. 8, 849–853.
Chandler, D.J., 2013. Something's got to give: psychiatric disease on the rise and novel drug development on the decline. Drug Discov. Today 18, 202–206.
Chaudhry, I.B., Hallak, J., Husain, N., Minhas, F., Stirling, J., Richardson, P., Dursun, S., Dunn, G., Deakin, B., 2012. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J. Psychopharmacol. 26, 1185–1193.
Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., Egan, M.F., Kleinman, J.E., Weinberger, D.R., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. 75, 807–821.
Chessick, C.A., Allen, M.H., Thase, M., Batista Miralha da Cunha, A.B., Kapczinski, F.F., de Lima, M.S., dos Santos Souza, J.J., 2006. Azapirones for generalized anxiety disorder. Cochrane Database Syst. Rev., 19.
Chevreul, K., Prigent, A., Bourmaud, A., Leboyer, M., Durand-Zaleski, I., 2013. The cost of mental disorders in France. Eur. Neuropharmacol. 23, 879–886.
Chico, L.K., Van Eldik, L.J., Watterson, D.M., 2009. Targeting protein kinases in central nervous system disorders. Nat. Rev. Drug Discov. 8, 802–809.
Choi, S.H., Kim, Y.H., Hebisch, M., Sliwinski, C., Lee, S., D'Avanzo, C., Chen, H., Hooli, B., Asselin, C., Muffat, J., Klee, J.B., Zhang, C., Wainger, B.J., Peitz, M., Kovacs, D.M., Woolf, C.J., Wagner, S.L., Tanzi, R.E., Kim, D.Y., 2014. A three-dimensional human neural cell culture model of Alzheimer's disease. Nature 515, 274–278.
Chiu, C.T., Wang, Z., Hunsberger, J.G., Chuang, D.M., 2013. Therapeutic potential of mood stabilizers lithium and Valproic acid: beyond bipolar disorder. Pharmacol. Rev. 65, 105–142.
Chuang, J.C., Zigman, J.M., 2010. Ghrelin's roles in stress, mood, and anxiety regulation. Int. J. Peptides 2010 (ID460549), 1–5.
Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M., Geddes, J.R., 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378, 1306–1315.
Cipriani, A., Koesters, M., Furukawa, T.A., Nosè, M., Purgato, M., Omori, M., Omori, I.M., Trespidi, C., Barbui, C., 2012. Duloxetine versus other anti-depressive agents for depression. Cochrane Database Syst. Rev., 10.
Clavenna, A., Cartabia, M., Sequi, M., Costantino, M.A., Bortolotti, A., Fortino, I., Merlino, L., Bonati, M., 2013. Burden of psychiatric disorders in the pediatric population. Eur. Neuropsychopharmacol. 23, 98–106.
Clay, H.B., Sillivan, S., Konradi, C., 2011. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. Int. J. Dev. Neurosci. 29, 311–324.
Clifton, N.E., Morisot, N., Girardon, S., Millan, M.J., Loiseau, F., 2013. Enhancement of social novelty discrimination by positive allosteric modulators at metabotropic glutamate 5 receptors: adolescent administration prevents adult-onset deficits induced by neonatal treatment with phencyclidine. Psychopharmacology 225, 579–594.
Cloninger, C.R., 2006. The science of well-being: an integrated approach to mental health and its disorders. World Psychiatry 5, 71–76.

Clutton-Brock, T., Sheldon, B.C., 2010. Individuals and populations: the role of long-term, individual-based studies of animals in ecology and evolutionary biology. Trends Ecol. Evol. 25, 562–573.
Cole, J.O., 1964. Therapeutic efficacy of antidepressant drugs: a review. J. Am. Med. Assoc. 190, 448–455.
Cole, M.W., Anticevic, A., Repovs, G., Barch, D., 2011. Variable global dysconnectivity and individual differences in schizophrenia. Biol. Psychiatry 70, 43–50.
Coles, M.E., Coleman, S.L., 2010. Barriers to treatment seeking for anxiety disorders: initial data on the role of mental health literacy. Depress. Anxiety 27, 63–71.
Collins, P.Y., Insel, T.R., Chockalingam, A., Daar, A., Maddox, Y.T., 2013. Grand challenges in global mental health: integration in research, policy, and practice. PLoS Med. 10, e1001434.
Comley, J., 2013. Outsourced kinase profiling services – adding value to in-house kinase programmes. Drug Discov. World (Fall), 26–34.
Comley, J., 2014. The current status of non-biopharma drug discovery. Drug Discov. World (Spring), 62–69.
Conn, P.J., Lindsley, C.W., Meiler, J., Niswender, C.M., 2014. Opportunities and challenges in the discovery of allosteric modulators of GPCRs for treating CNS disorders. Nat. Rev. Drug Discov. 13, 692–708.
Connolly, K.R., Thase, M.E., 2012. Emerging drugs for major depressive disorder. Expert Opin. Emerg. Drugs 17, 105–126.
Connor, D.F., Arnsten, A.F., Pearson, G.S., Greco, G.F., 2014. Guanfacine extended release for the treatment of attention-deficit/hyperactivity disorder in children and adolescents. Expert Opin. Pharmacother. 15, 1601–1610.
Cook, D., Nuro, E., Murai, K.K., 2014. Increasing our understanding of human cognition through the study of Fragile X Syndrome. Dev. Neurobiol. 74, 147–177.
Cooper, W.O., Habel, L.A., Sox, C.M., Chan, K.A., Arbogast, P.G., Cheetham, T.C., Murray, K.T., Quinn, V.P., Stein, C.M., Callahan, S.T., Fireman, B.H., Fish, F.A., Kirshner, H.S., O'Duffy, A., Connell, F.A., Ray, W.A., 2011. ADHD drugs and serious cardiovascular events in children and young adults. New Engl. J. Med. 365, 1896–1904.
Copeland, W., Shanahan, L., Costello, J., Angold, A., 2011. Cumulative prevalence of psychiatric disorders by young adulthood: a prospective cohort analysis form the great smoky mountain study. J. Am. Child Adolesc. Psychiatry 50, 252–261.
Coppen, A., 1967. The biochemistry of affective disorders. Br. J. Psychiatry 113, 1236–1264.
Corrêa Coutinho, F., Pereira Dias, G., do Nascimento Bevilaqua, M.C., Gardino, P.F., Pimentel Rangé, B., Nardi, A.E., 2010. Current concept of anxiety: implications form Darwin to the DSM-V for the diagnosis of generalized anxiety disorder. Expert Rev. Neurother. 10, 1307–1320.
Correll, C.U., Kratochvil, C.J., March, J.S., 2011. Developments in pediatric psychopharmacology: focus on stimulants, antidepressants, and antipsychotics. J. Clin. Psychiatry 72, 655–670.
Cotton, G., Bowen, W., Grundy, R., Hass, U., 2013. Fluorescence lifetime assays. Drug Discov. World (Fall), 79–86.
Crane, G.E., 1957. Iproniazid (marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. Psychiatry Res. Rep. Am. Psychiatr. Assoc. 8, 142–152.
Creese, I., Burt, D.R., Snyder, S.H., 1976. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 192, 481–483.
Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381, 1371–1379.
Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S.D., Andersson, G., 2010. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. Clin. Psychol. Rev. 30, 51–62.
Cummings, J.L., 2009. Defining and labeling disease-modifying treatments for Alzheimer's disease. Alzheimer's Dementia 5, 406–418.
Cunningham, M.G., Goldstein, M., Katz, D., Quimby O'Neil, S., Joseph, A., Price, B., 2006. Coalescence of psychiatry, neurology, and neuropsychology: from theory to practice. Harv. Rev. Psychiatry 14, 127–140.
Cuthbert, B.N., Insel, T.R., 2010. Toward new approaches to psychotic disorders: the NIMH research domain criteria project. Schizophr. Bull. 36, 1061–1062.
Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 11, 126.
Cuthbert, B.N., 2014. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 13, 28–35.
Cyr, M., Brown, C.S., 1998. Current drug therapy recommendations for the treatment of attention deficit hyperactivity disorder. Drugs 56, 215–223.
Czeh, B., Di Benedetto, B., 2012. Antidepressants act directly on astrocytes: evidence and functional consequences. Eur. Neuropsychopharmacol. 23, 171–185.
Dahlin, J.L., Walters, M.A., 2014. The essential roles of chemistry in high-throughput screening triage. Future Med. Chem. 6, 1265–1290.
Daker-White, G., Rogers, A., 2013. What is the potential for social networks and support to enhance future telehealth interventions for people with a diagnosis of schizophrenia: a critical interpretive synthesis. BMC Psychiatr. 13, 279.
Dahlström, A., Fuxe, K., 1964. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand. 232, 1–55.
Dallaspezia, S., Benedetti, F., 2009. Melatonin, circadian rhythms, and the clock genes in bipolar disorder. Curr. Psychiatr. Rep. 11, 488–493.
Davidson, M.A., 2008. ADHD in adults: a review of the literature. J. Atten. Disord. 11, 628–641.
Davidson, J.R., 2006. Pharmacotherapy of social anxiety disorder: what does the evidence tell us? J Clin Psychiatry. 67: Suppl 12, 20-26.
Davies, M., Newell, J.G., Derry, J.M., Martin, I.L., Dunn, S.M., 2000. Characterization of the interaction of zopiclone with gamma-aminobutyric acid type A receptors. Mol. Pharmacol. 58, 756–762.
Davis, J.C., Furstenthal, L., Desai, A.A., Norris, T., Suraria, S., Fleming, E., Ma, P., 2009. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nat. Rev. Drug Discov. 8, 279–286.
Davis, J.M., Glakas, W.J., Qu, J., Prasad, P., Leucht, S., 2011. Should we treat depression with drugs or psychological interventions? A reply to Ioannidis. Philos. Ethics Humanit. Med. 6, 1–13.
Dawson, G.R., Collinson, N., Atack, J.R., 2005. Development of subtype selective GABAA modulators. CNS Spectr. 10, 21–27.
Dean, B., 2009. Is schizophrenia the price of human central nervous system complexity? Aust. N. Z. J. Psychiatry 43, 13–24.
Dean, B., Moller, H.-J., Svensson, T.H., Geyer, M.A., Rujescu, D., Scarr, E., Millan, M.J., 2013. Problems and solutions to filling the drying drug pipeline for psychiatric disorders: a report from the inaugural 2012 CINP think tank. Int. J. Neuropsychopharmacol. 17, 137–148.
Deco, G., Kringelbach, M.L., 2014. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron 84, 892–905.
De Bodinat, C., Guardiola-Lemaitre, B., Mocaër, E., Renard, P., Muñoz, M.J., Millan, M.J., 2010. Agomelatine, the first

melatonergic antidepressant: discovery, characterization and development. Nat. Rev. Drug Discov. 2010 (9), 628–642.
De Jaegher, H., Di Paolo, E., Gallagher, S., 2010. Can social interaction constitute social cognition? Trends Cogn. Sci. 14, 441–447.
Dekeyne, A., Mannoury la Cour, C., Gobert, A., Brocco, M., Lejeune, F., Serres, F., Sharp, T., Daszuta, A., Soumier, A., Papp, M., Rivet, J.M., Flik, G., Cremers, T.I., Muller, O., Lavielle, G., Millan, M.J., 2008. S32006, a novel 5-HT2C receptor antagonist displaying broad-based antidepressant and anxiolytic properties in rodent models. Psychopharmacology 199, 549–568.
Delay, J., Deniker, P., 1952. Le traitement des psychoses par une méthode neurolytique dérivée d´hibernothérapie, le 4560R.P. utilisé seul en cure prolongée et continue. C.R. Congr. alién. Neur. France 50, 497–502.
Delay, J., Deniker, P., Harl, J.M., 1952. Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale élective (4560 RP). Ann. Med. Psychol. 2, 112–117.
De Ponti, F., Poluzzi, E., Cavalli, A., Recanatini, M., Montanaro, N., 2002. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. Drug Saf. 25, 263–286.
Depp, C.A., Ceglowski, J., Wang, V.C., Yaghouti, F., Mausbach, B.T., Thompson, W.K., Granholm, E.L., 2014. Augmenting psychoeducation with a mobile intervention for bipolar disorder: A randomized controlled trial. J. Affect. Disord. 174C, 23–30.
DeRubeis, R.J., Siegle, G.J., Hollon, S.D., 2008. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat. Rev. Neurosci. 9, 788–796.
Desbonnet, L., O'Tuathaigh, C., Clarke, G., O'Leary, C., Petit, E., Clarke, N., Tighe, O., Lai, D., Harvey, R., Cryan, J.F., Dinan, T.G., Waddington, J.L., 2012. Phenotypic effects of repeated psychosocial stress during adolescence in mice mutant for the schizophrenia risk gene neuregulin-1: a putative model of gene × environment interaction. Brain Behav. Immun. 26, 660–671.
De Souza, E.B., Cload, S.T., Pendergrast, P.S., Sah, D.W.Y., 2009. Novel therapeutic modalities to address nondrugable protein interaction targets. Neuropsychopharmacol. Rev. 34, 142–158.
Devoy, A., Bunton-Stasyshyn, R.K.A., Tybulewicz, V.L.J., Smith, A.J.H., Fisher, E.M.C., 2012. Genomically humanized mice: technologies and promises. Nat. Rev. Genet. 13, 14–20.
Dew, R.E., Kollins, S.H., 2010. Lisdexampfetamine dimesylate: a new option in stimulant treatment for ADHD. Expert Opin Pharmacother. 11, 2907–2913.
Di Benedetto, B., Rupprecht, R., Czéh, B., 2013. Talking to the synapse: how antidepressants can target glial cells to reshape brain circuits. Curr. Drug Targets 14, 1329–1335.
Di Luca, M., Baker, M., Corradetti, R., Kettenmann, H., Mendlewicz, J., Olesen, J., Ragan, I., Westphal, M., 2011. Consensus document on European brain research. Eur. J. Neurosci. 33, 768–818.
Di Masi, J.A., Grabowski, H.G., 2007. The cost of biopharmaceutical R&D: is biotech different? Manage. Decis. Econ. 28, 469–479.
Dimond, P., Carlson, K., Bouvier, M., Gerard, C., Xu, L., Covic, L., Agarwal, A., Ernst, O.P., Janz, J.M., Schwartz, T.W., Gardella, T.J., Milligan, G., Kuliopulos, A., Sakmar, T.P., Hunt, S.W., 2011. G protein-coupled receptor modulation with pepducins: moving closer to the clinic. Ann. NY Acad. Sci. USA 1226, 34–49.
Doehrmann, O., Ghosh, S.S., Polli, F.E., Reynolds, G.O., Horn, F., Keshavan, A., Triantafyllou, C., Saygin, Z.M., Whitfield-Gabrieli, S., Hofman, S.G., Pollack, M., Gabrieli, J.D., 2013. Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. JAMA Psychiatry 70, 87–97.
Doherty, J.L., Owen, M.J., 2014. Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. Genome Med. 2014 Apr 28;6(4):29. http://dx.doi.org/10.1186/gm546.
Dolgin, E., 2014. Massive schizophrenia genomics study offers new drug directions. Nat. Rev. Drug Discov. 13, 641–643.
Douglas, V.I., 1972. Stop, look, and listen: The problem of sustained attention and impulse control in hyperactive and normal children. Canad. J. Behav. Sci. 4, 259–282.
Downs, M., Blackburn, T., 2012. The challenges of the changing drug discovery model. Drug Discov. World (Fall), 9–16.
Dragalin, V., 2011. An introduction to adaptive designs and adaptation in CNS trials. Eur. Neuropsychopharmacol. 21, 153–158.
Drews, J., 2003. Strategic trends in the drug industry. Drug Discov. Today 8, 411–420.
Drews, J., 2006. What's in a number? Nat. Rev. Drug Discov. 5, 975.
D'Souza, D.C., Singh, N., Elander, J., Carbuto, M., Pittman, B., Udo de Haes, J., Sjogren, M., Peeters, P., Ranganathan, M., Schipper, J., 2012. Glycine transporter inhibitor attenuates the psychotomimetic effects of ketamine in healthy males: preliminary evidence. Neuropsychopharmacology, 37; , 1036–1046.
Du, J., Suzuki, K., Wei, Y., Wang, Y., Blumenthal, R., Chen, Z., Falke, C., Zarate Jr, C.A., Manji, H.K., 2007. The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. Neuropsychopharmacology 32, 793–802.
Du, Z.D., Wang, R., Prakash, R., Chaudhury, S., Dayananda, G., 2012. Transcranial magnetic stimulation in schizophrenia: the contribution of neuroimaging. Curr. Top. Med. Chem. 12, 2452–2457.
Dudchenko, P.A., Talpos, J., Young, J., Baxter, M.G., 2012. Animal models of working memory: a review of tasks that might be used in screening drug treatments for the memory impairments found in schizophrenia. Neurosci. Biobehav. Rev. 37, 2111–2124.
Duman, R.S., Voleti, B., 2012. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci. 35, 47–56.
Durstewitz, D., Seamans, J.K., 2008. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. Biol. Psychiatry 64, 739–749.
Dwyer, J.M., Lepack, A.E., Duman, R.S., 2012. mTOR activation is required for the antidepressant effects of mGluR2/3 blockade. Int. J. Neuropsychopharmacol. 15, 429–434.
Ehninger, D., Li, W., Fox, K., Stryker, M.P., Silva, A.J., 2008. Reversing neurodevelopmental disorders in adults. Neuron 60, 950–960.
Eichler, H.G., Bloechl-Daum, B., Brasseur, D., Breckenridge, A., Leufkens, H., Raine, J., Salmonson, T., Schneider, C.K., Rasi, G., 2013. The risks of risk aversion in drug regulation. Nat. Rev. Drug Discov. 12, 907–916.
Ellwardt, E., Zipp, F., 2014. Molecular mechanisms linking neuroinflammation and neurodegeneration in MS. Exp. Neurol. 262PA, 8–17.
Emery, N.J., Clayton, N.S., 2004. The mentality of crows: convergent evolution of intelligence in corvids and apes. Science 306, 1903–1907.
Emery, N.J., Clayton, N.S., 2009. Comparative social cognition. Annu. Rev. Psychol. 60, 87–113.
Eppig, C., Fincher, C.L., Thornhill, R., 2010. Parasite prevalence and the worldwide distribution of cognitive ability. Proc. R. Soc. B 277, 3801–3808.
Enck, P., Bingel, U., Schedlowski, M., Rief, W., 2013. The placebo response in medicine: minimize, maximize or personalize? Nat. Rev. Drug Discov. 12, 191–204.
English, B., Thomas, K., Johnstone, J., Bazih, A., Gertsik, L., Ereshefsky, L., 2014. Use of translational pharmacodynamic biomarkers in early-phase clinical studies for schizophrenia. Biomark. Med. 8, 29–49.

Enna, S.J., Williams, M., 2009. Challenges in the search for drugs to treat central nervous system disorders. J. Pharmacol. Exp. Ther. 329, 404–411.
Espuny-Camacho, I., Michelsen, K.A., Gall, D., Linaro, D., Hasche, A., Bonnefont, J., Ball, C., Orduz, D., Bilheu, A., Herpoel, A., Lambert, N., Gaspard, N., Péron, S., Schiffmann, S.N., Giugliano, M., Gaillard, A., Vanderhaeghen, P., 2013. Pyramidal neurons derived from human pluripotent stem cells integrate efficiently into mouse brain circuits in vivo. Neuron 77, 440–456.
Evers, K., 2009. Personalized medicine in psychiatry: ethical challenges and opportunities. Dialog. Clin. Neurosci. 11, 427–434.
Eyding, D., Leigemann, M., Grouven, U., et al., 2010. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. Br. Med. J. 341, c4737.
Fagervall, I., Ross, S.B., 1986. Inhibition of monoamine oxidase in monoaminergic neurones in the rat brain by irreversible inhibitors. Biochem. Pharmacol. 35, 1381–1387.
Felt, B.T., Biermann, B., Christner, J.G., Kochhar, P., Harrison, R.V., 2014. Diagnosis and management of ADHD in children. Am. Fam. Physician 90, 456–464.
Fernández, J., Alonso, J.M., Andrés, J.I., Cid, J.M., Díaz, A., Iturrino, L., Gil, P., Megens, A., Sipido, V.K., Trabanco, A.A., 2005. Discovery of new tetracyclic tetrahydrofuran derivatives as potential broad-spectrum psychotropic agents. J. Med. Chem. 48, 1709–1712.
Fiedorowicz, J.G., Swartz, K.L., 2004. The role of monoamine oxidase inhibitors in current psychiatric practice". J. Psychiatr. Pract. 10, 239–248.
Findling, R.L., 2008. Evolution of the treatment of attention-deficit-hyperactivity disorder in children: a review. Clin. Ther. 30, 942–957.
Fineberg, N.A., Gale, T.M., 2005. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int. J. Neuropsychopharmacol. 8, 107–129.
Fjell, A.M., McEvoy, L., Holland, D., Dale, A.M., Walhovd, K.B., 2014. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Alzheimer's Disease Neuroimaging Initiative. Prog. Neurobiol. 117, 20–40.
Fleischhacker, W.W., Burns, T., European Group For Research In Schizophrenia, 2002. Feasibility of placebo-controlled clinical trials of antipsychotic compounds in Europe. Psychopharmacology 162, 82–84.
Foley, K.F., DeSanty, K.P., Kast, R.E., 2006. Bupropion: pharmacology and therapeutic applications. Expert Rev. Neurother. 6, 1249–1265.
Folsom, T.D., Fatemi, S.H., 2013. The involvement of Reelin in neurodevelopmental disorders. Neuropharmacology 68, 122–135.
Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lançon, C., Brittner, M., Micoulaud-Franchi, J.A., Richieri, R., Courtet, P., Abbar, M., Roger, M., Leboyer, M., Boyer, L., 2014. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology 231, 3663–3676.
Ford, J.M., Morris, S.E., Hoffman, R.E., Sommer, I., Waters, F., McCarthy-Jones, S., Thoma, R.J., Turner, J.A., Keedy, S.K., Badcock, J.c., Cuthbert, B.N., 2014. Studying hallucinations within the NIMH RDoC framework. Schizophr. Bull. 40, S295–S304.
Fornito, A., Bullmore, E.T., 2015. Connectomics: a new paradigm for understanding brain disease. Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2014.02.011.
Fossat, P., Turpin, F.R., Sacchi, S., Dulong, J., Shi, T., Rivet, J.M., Sweedler, J.V., Pollegioni, L., Millan, M.J., Oliet, S.H., Mothet, J.P., 2012. Glial D-serine gates NMDA receptors at excitatory synapses in prefrontal cortex. Cereb. Cortex 22, 595–606.
Foster, J.A., McVey Neufeld, K.A., 2013. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 36, 305–312.
Foussias, G., Agid, O., Fervaha, G., Remington, G., 2014. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. Eur. Neuropsychopharmacol. 24, 693–709.
Fox, M.D., Buckner, R.L., White, M.P., Greicius, M.D., Pascual-Leone, A., 2012. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol. Psychiatry 72, 595–603.
Frampton, J.E., 2011. Vilazodone in major depressive disorder. CNS Drugs 25, 615–627.
Franck, M.J., Fossella, J.A., 2011. Neurogenetics and pharmacology of learning, motivation, and cognition. Neuropsychopharmacology 36, 133–152.
Fromer, M., Pocklington, A.J., Kavanagh, D.H., Williams, H.J., Dwyer, S., Gormley, P., Georgieva, L., Rees, E., Palta, P., Ruderfer, D.M., Carrera, N., Humphreys, I., Johnson, J.S., Roussos, P., Barker, D. D., Banks, E., Milanova, V., Grant, S.G., Hannon, E., Rose, S.A., Chambert, K., Mahajan, M., Scolnick, E.M., Moran, J.L., Kirov, G., Palotie, A., McCarroll, S.A., Holmans, P., Sklar, P., Owen, M.J., Purcell, S.M., O'Donovan, M.C., 2014. De novo mutations in schizophrenia implicate synaptic networks. Nature 506, 179–184.
Fu, C.H., Costafreda, S.G., 2013. Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. Can. J. Psychiatry 58, 499–508.
Fuller, R.W., Wong, D.T., Robertson, D.W., 1991. Fluoxetine, a selective inhibitor of serotonin uptake. Med. Res. Rev. 11, 17–34.
Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkötter, J., McGuire, P., Yung, A., 2013. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70, 107–120.
Gabrielsson, J., Dolgos, H., Gillberg, P.G., Bredberg, U., Benthem, B., Duker, G., 2009. Early integration of pharmacokinetic and dynamic reasoning is essential for optimal development of lead compounds: strategic considerations. Drug Discov. Today 14, 358–372.
Gaj, T., Gersbach, C.A., Barbas, C.F., 2013. ZFN, TALEN, and CRISPR/Cas-based method for genome engineering. Trends Biotechnol. 31, 397–405.
Galizzi, J.P., Lockhart, B.P., Bril, A., 2013. Applying systems biology in drug discovery and development. Drug Metabol. Drug Interact. 28, 67–78.
Gamber, K.M., 2014. The CRISPR/Cas9 system: cutting a path for rapid generation of more translational animal models. Drug Discov. World (Summer), 37–41.
Garcia-Ribera, C., Bulbena, A., 2011. Determinants of medicine-taking in psychiatric patients. Curr. Clin. Pharmacol. 6, 100–107.
Garnock-Jones, K.P., Keating, G.M., 2009. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. Paediatr. Drugs 11, 203–226.
Gass, N., Cleppien, D., Zheng, L., Schwarz, A.J., Meyer-Lindenberg, A., Vollmayr, B., Sartorius, A., 2013. Functionally altered neurocircuits in a rat model of treatment-resistant depression show prominent role of the habenula. Eur. Neuropsychopharmacol. 24, 381–390.
Gavin, D.P., Floreani, C., 2014. Epigenetics of schizophrenia: an open and shut case. Int. Rev. Neurobiol. 115, 155–201.
Geerts, H., 2011. Mechanistic disease modeling as a useful tool for improving CNS drug research and development. Drug Dev. Res. 72, 66–73.

Geerts, H., 2012. α7 nicotinic receptor modulators for cognitive deficits in schizophrenia and Alzheimer's disease. Expert Opin. Investig. Drugs 21, 59–65.
Geerts, H., Spiros, A., Roberts, P., Twyman, R., Alphs, L., Grace, A. A., 2012. Blinded prospective evaluation of computer-based mechanistic schizophrenia disease model for predicting drug response. PLos One 7, e49732.
Gelenberg, A.J., Thase, M.E., Meyer, R.E., Goodwin, F.K., Katz, M. M., Chmura Kraemer, H., Potter, W.Z., Shelton, R.C., Fava, M., Khan, A., Trivedi, M.H., Ninan, P.T., Mann, J.J., Bergeson, S., Endicott, J., Kocsis, J.H., Leon, A.C., Manji, H.K., Rosenbaum, J.f., 2008. The history and current state of antidepressant clinical trial design: a call to action for proof-of-concept studies. J. Clin. Psychiatry 69, 1513–1528.
GENDEP Investigators, MARS Investigators, STARD Investigators, 2013. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. Am. J. Psychiatry 170, 207–217.
Gershon, S., Trautner, E.M., 1956. The treatment of shock-dependency by pharmacological agents. Med. J. Aust. 1, 783–787.
Gobert, A., Rivet, J.M., Billiras, R., Parsons, F., Millan, M.J., 2011. Simultaneous quantification of D- vs. L-serine, taurine, kynurenate, phosphoethanolamine and diverse amino acids in frontocortical dialysates of freely-moving rats: differential modulation by N-methyl-D-aspartate (NMDA) and other pharmacological agents. J. Neurosci. Methods 202, 143–157.
Goldman, M., 2012. The innovative medicines initiative: a European response to the innovation challenge. Clin. Pharmacol. Ther. 91, 418–425.
Goldman, D., Domschke, K., 2014. Making sense of deep sequencing. Int. J. Neuropsychopharmacol. 17, 1717–1725.
Goldstein, B.L., Klein, D.N., 2014. A review of selected candidate endophenotypes for depression. Clin. Psychol. Rev. 34, 417–427.
Gorman, A.M., Healy, S.J., Jäger, R., Samali, A., 2012. Stress management at the ER: regulators of ER stress-induced apoptosis. Pharmacol. Ther. 134, 306–316.
Gould, T.D., Manji, H.K., 2005. Glycogen Synthase Kinase-3: a putative molecular target for lithium mimetic drugs. Neuropsychopharmacology 30, 1223–1237.
Goyal, M., Singh, S., Sibinga, E.M., Gould, N.F., Rowland-Seymour, A., Sharma, R., Berger, Z., Sleicher, D., Maron, D.D., Shihab, H. M., Ranasinghe, P.D., Linn, S., Saha, S., Bass, E.B., Haythornthwaite, J.A., 2014. Mediation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern. Med. 174, 357–368.
Grabrucker, A.M., Schmeisser, M.J., Schoen, M., Boeckers, T.M., 2011. Postsynaptic proSAP/shank scaffolds in the cross-hairs of synaptopathies. Trends Cell Biol. 21, 594–603.
Granger, P., Biton, B., Faure, C., Vige, X., Depoortere, H., Graham, D., Langer, S.Z., Scatton, B., Avenet, P., 1995. Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. Mol. Pharmacol. 47, 1189–1196.
Granholm, E., Ben-Zeev, D., Link, P.C., Bradshaw, K.R., Holden, J. L., 2012. Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. Schizophr. Bull. 38, 414–425.
Graur, D., Zheng, Y., Price, N., Azevedo, R.B.R., Zufall, R.A., Elhaik, E., 2013. On the immortality of television sets: "function" in the human genome according to the evolution-free Gospel of ENCODE. Genome Biol. 5, 578–590.
Grayson, D.R., Guidotti, A., 2012. The dynamics of DNA methylation in schizophrenia and related psychiatric disorders. Neuropsychopharmacology 38, 138–166.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.
Greene, C.S., Penrod, N.M., Williams, S.M., Moore, J.H., 2009. Failure to replicate a genetic association may provide important clues about genetic architecture. PLoS One 4, e5639.
Green, M., Hudson-Farmer, K., 2013. The repositioning revolution: save me from extinction to find me pastures new. Drug Discov. World 14 (Winter), 22–27.
Glausier, J.R., Lewis, D.A., 2013. Dendritic spine pathology in schizophrenia. Neuroscience 251, 90–107.
Glennon, J., Purper-Ouakil, D., Bakker, M., Zuddas, A., Hoekstra, P., Schulze, U., Castro-Fornieles, J., Santosh, P.J., Arango, C., Kölch, M., Coghill, D., Flamarique, I., Penzol, M.J., Wan, M., Murray, M., Wong, I.C., Danckaerts, M., Bonnot, O., Falissard, B., Masi, G., Fegert, J.M., Vicari, S., Carucci, S., Dittmann, R. W., Buitelaar, J.K., PERS Consortium, 2014. Paediatric European Risperidone Studies (PERS): context, rationale, objectives, strategy, and challenges. Eur. Child Adolesc. Psychiatry 23, 1149–1160.
Greggor, A.L., Clayton, N.S., Phalan, B., Thornton, A., 2014. Comparative cognition for conservationists. Trends Ecol. Evol. 29, 489–495.
Griebel, G., Holmes, A., 2013. 50 years of hurdles and hope in anxiolytic drug discovery. Nat. Rev. Drug Discov. 12, 667–687.
Gross, M.D., 1995. Origin of stimulant use for treatment of attention deficit disorder [letter]. Am. J. Psychiatr. 152, 298–299.
Grozeva, D., Kirov, G., Conrad, D.F., Barnes, C.P., Hurles, M., Owen, M.J., O'Donovan, M.C., Craddock, N., 2013. Reduced burden of very large and rare CNVs in bipolar affective disorder. Bipolar Disord. 15, 893–908.
Guardiola-Lemaitre, B., De Bodinat, C., Delagrange, P., Millan, M. J., Munoz, C., Mocaër, E., 2014. Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. Br. J. Pharmacol. 171, 3604–3619.
Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., Dodel, R., Ekman, M., Faravelli, C., Fratiglioni, L., Gannon, B., Jones, D.H., Jennum, P., Jordanova, A., Jönsson, L., Karampampa, K., Knapp, M., Kobelt, G., Kurth, T., Lieb, R., Linde, M., Ljungcrantz, C., Maercker, A., Melin, B., Moscarelli, M., Musayev, A., Norwood, F., Preisig, M., Pugliatti, M., Rehm, J., Salvador-Carulla, L., Schlehofer, B., Simon, R., Steinhausen, H.C., Stovner, L.J., Vallat, J.M., Van den Bergh, P., van Os, J., Vos, P., Xu, W., Wittchen, H.U., Jönsson, B., Olesen, J., CDBE2010 Study Group, 2011. Cost of disorders of the brain in Europe 2010. Eur. Neuropharmacol. 21, 718–779.
Guttmacher, A.E., McGuire, A.L., Ponder, B., Stefansson, K., 2010. Personalized genomic information: preparing for the future of genetic medicine. Nat. Rev. Genet. 11, 161–165.
Guy, J., Gan, J., Selfridge, J., Cobb, S., Bird, A., 2007. Reversal of neurological defects in a mouse model of Rett syndrome. Science 315, 1143–1147.
Hall, H., Ogren, S.O., 1981. Effects of antidepressant drugs on different receptors in the brain. Eur. J. Pharmacol. 70, 393–407.
Hampton, T., 2014. European-led project strives to simulate the human brain. J. Am. Med. Assoc. 311, 1598–1600.
Hånell, A., Marklund, N., 2014. Structured evaluation of rodent behavioral tests used in drug discovery research. Front. Behav. Neurosci. 8, 252.
Harrison, V., Proudfoot, J., Wee, P.P., Parker, G., Pavlovic, D.H., Manicavasagar, V., 2011a. Mobile mental health: review of the emerging field and proof of concept study. J. Ment. Health 20, 509–524.
Hariri, A.R., 2009. The neurobiology of individual differences in complex behavioral traits. Annu. Rev. Neurosci. 32, 225–247.
Harmer, C.J., Cowen, P.J., Goodwin, G.M., 2011. Efficacy markers in depression. J. Psychopharmacol. 25, 1148–1158.

Haro, J.M., Ayuso-Mateos, J.L., Bitter, I., Demotes-Mainard, J., Leboyer, M., Lewis, S.W., Linszen, D., Maj, M., McDaid, D., Meyer-Lindenberg, A., Robbins, T.W., Schumann, G., Thornicroft, G., Van Der Feltz-Cornelis, C., Van Os, J., Wahlbeck, K., Wittchen, H.U., Wykes, T., Arango, C., Bickenbach, J., Brunn, M., Cammarata, P., Chevreul, K., Evans-Lacko, S., Finocchiaro, C., Fiorillo, A., Forsman, A.K., Hazo, J.B., Knappe, S., Kuepper, R., Luciano, M., Miret, M., Obradors-Tarragó, C., Pagano, G., Papp, S., Walker-Tilley, T., 2014. ROAMER: roadmap for mental health research in Europe. Int. J. Methods Psychiatr. Res., 23; , 1–14.

Harris, S.E., Deary, I.J., 2011. The genetics of cognitive ability and cognitive ageing in healthy older people. Trends Cogn. Sci. 15, 388–394.

Harrison, P.J., 2015. The current and potential impact of genetics and genomics on neuropsychopharmacology. Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2013.02.005.

Harrison, V., Proudfoot, J., Wee, P.P., Parker, G., Pavlovic, D.H., Manicavasagar, V., 2011b. Mobile mental health: review of the emerging field and proof of concept study. J. Ment. Health 20, 509–524.

Hart, B.L., Hart, L.A., Pinter-Wollman, N., 2008. Large brains and cognition: where do elephants fit in? Neurosci. Biobehav. Rev. 32, 86–98.

Hasan, S., Bonde, B.K., Buchan, N.S., Hall, M.D., 2012. Network analysis has diverse roles in drug discovery. Drug Discov. Today 17, 869–874.

Hashimoto, K., Malchow, B., Falkai, P., Schmitt, A., 2013. Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. Eur. Arch. Psychiatry Clin. Neurosci. 263, 367–377.

Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., Manji, H.K., 2006b. Toward constructing an endophenotype strategy for bipolar disorders. Biol. Psychiatry 60, 93–105.

Hayden, E.C., 2014. Universities seek to boost industry partnerships: as drug companies shift focus, academia ramps up its role in bringing discoveries to market. Nature 509, 146.

Hayley, S., Litteljohn, D., 2013. Neuroplasticity and the next wave of antidepressant strategies. Front. Cell Neurosci. 7, 218.

Heal, DJ, Smith, SL, Gosden, J, Nutt, DJ., 2013. Amphetamine, past and present – a pharmacological and clinical perspective. J Psychopharmacol. 27, 479–496.

Healy, D., 1997. The Antidepressant Era. Harvard University Press, Cambridge, MA, 317.

Heidbreder, C.A., Newman, A.H., 2010. Current perspectives on selective dopamine D3 receptor antagonists as pharmacotherapeutics for addictions and related disorders. Ann. NY Acad. Sci. 1187, 4–34.

Heilker, R., Wolff, M., Tautermann, C.S., Bieler, M., 2009. G-protein-coupled receptor-focused drug discovery using a target class platform approach. Drug Discov. Today 14, 231–240.

Henry, T.R., 2003. The history of valproate in clinical neuroscience. Psychopharmacol. Bull. 37 (Suppl. 2), S5–S16.

Hevers, W., Lüddens, H., 1998. The diversity of GABAA receptors. Pharmacological and electrophysiological properties of GABAA channel subtypes. Mol. Neurobiol. 18, 35–86.

Hida, H., Mouri, A., Noda, Y., 2013. Behavioral phenotypes in schizophrenic animal models with multiple combinations of genetic and environmental factors. J. Pharmacol. Sci. 121, 185–191.

Hirao, K., Pontone, G.M., Smith, G.S., 2014. Molecular imaging of neuropsychiatric symptoms in Alzheimer's and Parkinson's disease. Neurosci. Biobehav. Rev. 49, 157–170.

Hoertnagl, C.M., Hofer, A., 2014. Social cognition in serious mental illness. Curr. Opin. Psychiatry 27, 197–202.

Hofmann, H.A., Beery, A.K., Blumstein, D.T., Couzin, I.D., Earley, R.L., Hayes, L.D., Hurd, P.L., Lacey, E.A., Phelps, S.M., Solomon, N.G., Taborsky, M., Young, L.J., Rubenstein, D.R., 2014. An evolutionary framework for studying mechanisms of social behavior. Trends Ecol. Evol. 29, 581–589.

Hollon, S.D., DeRubeis, R.J., Fawcett, J., Amsterdam, J.D., Shelton, R.C., Zajecka, J., Young, P.R., Gallop, R., 2014. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA Psychiatry 71, 1157–1164.

Holsboer, F., 1999. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. J. Psychiatr. Res. 33, 181–214.

Holtzheimer, P.E., Kosel, M., Schlaepfer, T., 2012. Brain stimulation therapies for neuropsychiatric disease. Handb. Clin. Neurol. 106, 681–695.

Hommers, L.G., Domschke, K., Deckert, J., 2015. Heterogeneity and individuality: microRNAs in mental disorders. J. Neural Transm. 122, 79–97.

Honey, G.D., Corlett, P.R., Absalom, A.R., Lee, M., Pomarol-Clotet, E., Murray, G.K., McKenna, P.J., Bullmore, E.T., Menon, D.D., Fletcher, P.C., 2008. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J. Neurosci. 28, 6295–6303.

Hounsou, C., Margathe, J.F., Oueslati, N., Belhocine, A., Dupuis, E., Thomas, C., Mann, A., Ilien, B., Rognan, D., Trinquet, E., Hibert, M., Pin, J.P., Bonnet, D., Durroux, T., 2014. Time-resolved FRET binding assay to investigate hetero-oligomer binding properties: proof of concept with dopamine D1/D3 heterodimer, ACS Chem. Biol.

Houslay, M.D., 2009. Disrupting specific PDZ domain-mediated interactions for therapeutic benefit. Br. J. Pharmacol. 158, 483–485.

Huang, L.C., Wu, X., Chen, J.Y., 2011. Predicting adverse side effects of drugs. BMC Genom. 12, S11.

Hubbard, R.E., 2011. Structure-based drug discovery and protein targets in the CNS. Neuropharmacology 60, 7–23.

Huffman, J.C., Stern, T.A., 2007. Neuropsychiatric consequences of cardiovascular medications. Dialogues Clin. Neurosci. 9, 29–45.

Huggins, D.J., Sherman, W., Tidor, B., 2012. Rational approaches to improving selectivity in drug design. J. Med. Chem. 55, 1424–1444.

Hunter, J., 2014. Collaboration for innovation is the new mantra for the pharmaceutical industry. Drug Discov.World (Spring), 9–15.

Hunziker, F., Fischer, E., Schmutz, J., 1967. 11-Amino-5H-dibenzo [b, e]-1, 4-diazepine. 10. Mitteilung über sieben gliedrige Heterocyclen. Helvet. Chim. Acta 50, 1588–1589.

Hyman, S.E., 2007. Can neuroscience be integrated into the DSM-V? Nat. Rev. Neurosci. 8, 725–732.

Hyman, S.E., 2010. The diagnosis of mental disorders: the problem of reification. Annu. Rev. Clin. 6, 155–179.

Ibrahim, L., Diazgranados, N., Franco-Chaves, J., Brutsche, N., Henter, I.D., Kronstein, P., Moaddel, R., Wainer, I., Luckenbaugh, D.A., Manji, H.K., Zarate, C.A., 2012a. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 37, 1526–1533.

Ibrahim, L., Diazgranados, N., Jolkovsky, L., Brutsche, N., Luckenbaugh, D.A., Herring, J., Potter, W.Z., Zarate, C.A., 2012b. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. J. Clin. Psychopharmacol. 32, 551–557.

Inoue, H., Yamanaka, S., 2011. The use of induced pluripotent stem cells in drug development. Clin. Pharmacol. Ther. 89, 655–661.

Insel, T.R., 2007. From animal models to model animals. Biol. Psychiatry 62, 1337–1339.

Insel, T.R., 2014. Brain somatic mutations: the dark matter of psychiatric genetics? Mol. Psychiatry. 19, 156–158.

Insel, T.R., 2014. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. Am. J. Psychiatry 171, 395–397.
Ioannidis, J.P., 2005. Why most published research findings are false. PLoS Med. 2, e124.
Ioannidis, J.P., 2014. How to make more published research true. PLoS Med. 11, e1001747.
IsHak, W.W., Mirocha, J., Pi, S., Tobia, G., Becker, B., Peselow, E. D., Cohen, R.M., 2014. Patient-reported outcomes before and after treatment of major depressive disorder. Dialogues Clin. Neurosci. 16, 171–183.
Ishibashi, T., Horisawa, T., Tokuda, K., Ishiyama, T., Ogasa, M., Tagashira, R., Matsumoto, K., Nishikawa, H., Ueda, Y., Toma, S., Oki, H., Tanno, N., Saji, I., Ito, A., Ohno, Y., Nakamura, M., 2010. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J. Pharmacol. Expert Ther. 334, 171–181.
Ishiyama, T., Tokuda, K., Ishibashi, T., Ito, A., Toma, S., Ohno, Y., 2007. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. Eur. J. Pharmacol. 572, 160–170.
Jack, C.R., Barrio, J.R., Kepe, V., 2013. Cerebral amyloid PET imaging in Alzheimer's disease. Acta Neuropathol. 126, 643–657.
Jacob, H.J., Lazar, J., Dwinell, M.R., Moreno, C., Geurts, A.M., 2010. Gene targeting in the rat: advances and opportunities. Trends Genet. 28, 510–518.
Janssen, P.A., Niemegeers, C.J., Schellekens, K.H., Lenaerts, F.M., 1967. Is it possible to predict the clinical effects of neuroleptic drugs (major tranquillizers) from animal data? IV. An improved experimental design for measuring the inhibitory effects of neuroleptic drugs on amphetamine-or apomorphine-induced "Cheroing" and "agitation" in rats. Arzneimittelforschung 17, 841–854.
Johnson, F.R., Van Houtven, G., Hass, S., White, J., Francis, G., Miller, D.W., Phillips, J.T., 2009. Multiple sclerosis patients' benefic-risk preferences: serious adverse event risks versus treatment efficacy. J. Neurol. 256, 554–562.
Jones, C.A., Watson, D.J., Fone, K.C., 2011. Animal models of schizophrenia. Br. J. Pharmacol. 164, 1162–1194.
Jorm, A.F., 2012. Mental health literacy: empowering the community to take action for better mental health. Am. Psychol. 67, 231–243.
Kaltenbach, T., 2014. Principles for winning digital health strategies. Drug Discov. World (Fall), 9–17.
Kalu, U.G., Sexton, C.E., Ebmeier, K.P., 2012. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol. Med. 42, 1791–1800.
Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison versus chlorpromazine/benztropine. Arch. Gen. Psychiatry 45, 789–796.
Karayiorgou, M., Flint, J., Gogos, J.A., Malenka, R.C., Genetic and Neural Complexity in Psychiatry 2011 Working Group, 2012. The best of times, the worst of times for psychiatric disease. Nat. Neurosci. 15, 811–812.
Karsenty, G., Ferron, M., 2012. The contribution of bone to whole-organism physiology. Nature 481, 314–320.
Kas, M.J., Fernandes, C., Schalkwyk, L.C., Collier, D.A., 2007. Genetics of behavioural domains across the neuropsychiatric spectrum; of mice and men. Mol. Psychiatry 12, 324–330.
Kas, M.J., Kahn, R.S., Collier, D.A., Waddington, J.L., Ekelund, J., Porteous, D.J., Schughart, K., Hovatta, I., 2011a. Translational neuroscience of schizophrenia: seeking a meeting of minds between mouse and man. Sci. Transl. Med. 3, 102mr3.
Kas, M.J., Krishnan, V., Gould, T.D., Collier, D.A., Olivier, B., Lesch, K.P., Domenici, E., Fuchs, E., Gross, C., Castrén, E., 2011b. Advances in multidisciplinary and cross-species approaches to examine the neurobiology of psychiatric disorders. Eur. Neuropsychopharmacol. 21, 532–544.
Kasper, S., McEwen, B.S., 2008. Neurobiological and clinical effects of the antidepressant tianeptine. CNS Drugs 22 (1), 15–26.
Kavoussi, R., 2006. Pregabalin: from molecule to medicine. Eur. Neuropsychopharmacol. 16, S128–S133.
Kawa, S., Giordano, J., 2012. A brief historicity of the diagnostic and statistical manual of mental disorders: issues and implications for the future of psychiatric canon and practice. Philos. Ethics Humanit. Med. 7, 2.
Keck, P.E., McElroy, S.L., 2003. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. Expert Opin. Investig. Drugs 12, 655–662.
Keefe, A.D., Pai, S., Ellington, A., 2010. Aptamers as therapeutics. Nat. Rev. Drug Discov. 9, 537–550.
Kehne, J.H., Cain, C.K., 2010. Therapeutic utility of non-peptidic CRF1 receptor antagonists in anxiety, depression, and stress-related disorderes: evidence from animal models. Pharmacol. Ther. 128, 460–487.
Keiser, M.J., Setola, V., Irwin, J.J., Laggner, C., Abbas, A.I., Hufeisen, S.J., Jensen, N.H., Kuijer, M.B., Matos, R.C., Tran, T.B., Whaley, R., Glennon, R.A., Hert, J., Thomas, K.L.H., Edwards, D.D., Shoichet, B.K., Roth, B.L., 2009. Predicting new molecular targets for known drugs. Nature 462, 175–181.
Keller, M.C., Miller, G., 2006. Resolving the paradox of common, harmful, heritable mental disorders: which evolutionary genetic models work best? Behav. Brain Sci. 29, 385–452.
Kempton, M.J., McGuire, P., 2015. How can neuroimaging facilitate the diagnosis and strafification of patients with psychosis? this issue, http://dx.doi.org/10.1016/j.euroneuro.2014.07.006.
Keseru, G.M., Makara, G.M., 2009. The influence of lead discovery strategies on the properties of drug candidates. Nat. Rev. Drug Discov. 8, 203–212.
Kessler, R.C., Ustun, T.B., 2004. Prevalence, severity, and unmet need for treatment of mental disorders in the world health organization world mental health surveys. J. Am. Med. Assoc. 291, 2581–2590.
Ketter, T.A., Manji, H.K., Post, R.M., 2003. Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. J. Clin. Psychopharmacol. 23, 484–495.
Khanna, I., 2012. Drug discovery in pharmaceutical industry: productivity challenges and trends. Drug Discov. Today 17, 1088–1102.
Khatib, F., DiMaio, F, Cooper, S., Kazmierczyk, M., Gilski, M., Krzywda, S., Zabranska, H., Pichova, I., Thompson, J., Popović, Z., Jaskolski, M., Baker, D., Foldit Void Crushers Group Foldit Contenders Group, 2011. Crystal structure of a monomeric retroviral protease solved by protein solving game players. Nat Struct Mol Biol., 18; , 1175–1177.
Khatib, F., DiMaio, F., Foldit Contenders Group, Foldit Void Crushers Group, Cooper, S., Kazmierczyk, M., Gilski, M., Krzywda, S., Zabranska, H., Pichova, I, Thompson, J., Popović, Z., Jaskolski, M., Baker, D., 2011. Crystal structure of a monomeric retroviral protease solved by protein folding game players. Nat. Struct. Mol. Biol. 18, 1175–1177.
Khoury, B., Langer, E.J., Pagnini, F., 2014. The DSM: mindful science or mindless power? a critical review. Front. Psychol. 5, 1–8.
Kielholz, P., 1979. Classification of depression and the activity profile of antidepressants. Prog. Neuro-psychopharmacol. Biol. Psychiatry 3, 59–63.
Kiloh, L.G., Ball, J.R., 1961. Depression treated with imipramine: a follow-up study. Br. Med. J. 1, 168–171.
Kinsey, B., 2014. Vaccines against drugs of abuse: where are we now? Ther. Adv. Vaccines 2, 106–117.
Kirchheiner, J., Nickchen, K., Bauer, M., Wong, M.L., Licinio, J., Roots, J., Brockmöller, J., 2004. Pharmacogenetics of

antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol. Psychiatry 9, 442–473.
Kirov, G., Rees, E., Walters, J.T., Escott-Price, V., Georgieva, L., Richards, A.L., Chambert, K.D., Davies, G., Legge, S.E., Moran, J.L., McCarroll, S.A., O'Donovan, M.C., Owen, M.J., 2013. The penetrance of copy number variations for schizophrenia and developmental delay. Biol. Psychiatry 75, 378–385.
Klengel, T., Pape, J., Binder, E.B., Mehta, D., 2014. The role of DNA methylation in stress-related psychiatric disorders. Neuropharmacology 80, 115–132.
Klöppel, S., Abdulkadir, A., Jack, C.R., Koutsouleris, N., Mourao-Miranda, J., Vemuri, P., 2012. Diagnostic neuroimaging across diseases. Neuroimage 61, 457–463.
Kneller, R., Mongeon, M., Cope, J., Garner, C., Ternouth, P., 2014. Industry-university collaborations in Canada, Japan, the UK and USA-with emphasis on publication freedom and managing the intellectual property lock-up problem. PLoS One 9, e90302.
Knuesel, I., 2010. Reelin-mediated signaling in neuropsychiatric and neurodegenerative diseases. Prog. Neurobiol. 91, 257–274.
Kocsis, J.H., Leon, A.C., Markowitz, J.C., Manber, R., Arnow, B., Klein, D.N., Thase, M.E., 2009. Patients preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. J. Clin. Psychiatry 70, 354–361.
Kofink, D., Boks, M.P.M., Timmers, H.T.M., Kas, M.J., 2013. Epigenetic dynamics in psychiatric disorders: environmental programming of neurodevelopmental processes. Neurosci. Biobehav. Rev. 37, 831–845.
Kokras, N., Dalla, C., 2014. Sex differences in animal models of psychiatric disorders. Br. J. Pharmacol. 171, 4595–4619.
Komossa, K., Rummel-Kluge, C., Schwarz, S., Schmid, F., Hunger, H., Kissling, W., Leucht, S., 2011. "Risperidone versus other atypical antipsychotics for schizophrenia". Cochrane Database Syst. Rev. (1)), CD006626.
Kotaleski, J.H., Blackwell, K.T., 2010. Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. Nat. Rev. Neurosci. 11, 239–251.
Krstic, D., Pfister, S., Notter, T., Knuesel, I., 2013. Decisive role of Reelin signaling during early stages of Alzheimer's disease. Neuroscience 246, 108–116.
Kuhn, R., 1957. Treatment of depressive states with an iminodibenzyl derivative (G 22355)]. Schweiz. Med. Wochenschr. 87, 1135–1140.
Kupfer, D.J., Kuhl, E.A., Wulsin, L., 2013. Psychiatry's integration with medicine: the role of DSM-5. Annu. Rev. Med. 64, 385–392.
Kurtz, M.M., 2012. Cognitive remediation for schizophrenia: current status, biological correlates and predictors of response. Expert. Rev. Neurother. 12, 813–821.
Labarthe, A., Fiquet, O., Hassouna, R., Zizzari, P., Lanfumey, L., Ramoz, N., Grouselle, D., Epelbaum, J., Tolle, V., 2014. Ghrelin-derived peptides: a link between appetite/reward, GH axis, and psychiatric disorders? Front. Endocrinol. 5, 163.
Laborit, H., Huegenard, P., 1951. L'hibernation artificielle par moyens pharmacodynamique set physiques en chirurgie. J. Chir. (M. Masson), 67, 631–641.
Lader, M., 2011. Benzodiazepines revisited-will we ever learn? Addiction 106, 2086–2109.
Lange, K.W., Reichl, S., Lange, K.M., Tucha, L., Tucha, O., 2010. The history of attention deficit hyperactivity disorder. Atten. Defic. Hyperact. Disord. 2, 241–255.
Lapidus, K.A., Soleimani, L., Murrough, J.W., 2013. Novel glutamatergic drugs for the treatment of mood disorders. Neuropsychiatr. Dis. Treat. 9, 1101–1112.
Larivière, V., Diepeveen, S., Chonaill, S.N., Macaluso, B., Pollitt, A., Grant, J., 2013. International comparative performance of mental health research, 1980–2011. Eur. Neuropsychopharmacol. 23, 1340–1347.
Lasagna, L., 1955. The controlled clinical trial: theory and practice. J Chronic Dis. 1, 353–367.
Lauzon, N.M., Laviolette, S.R., 2010. Dopamine D4-receptor modulation of cortical neuronal network activity and emotional processing: Implications for neuropsychiatric disorders. Behav. Brain Res. 208, 12–22.
Law, A.J., Wang, Y., Sei, Y., O'Donnell, P., Piantadosi, P., Papaleo, F., Straub, R.E., Huang, W., Thomas, C.J., Vakkalanka, R., Besterman, A.D., Lipska, B.K., Hyde, T.M., Harrison, P.J., Kleinman, J.E., Weinberger, D.R., 2012. Neuregulin 1-ErbB4-PI3K signaling in schizophrenia and phosphoinositide 3-kinase-p110δ inhibition as a potential therapeutic strategy. Proc. Natl. Acad. Sci. USA 109, 12165–12170.
Lawson, A.D.G., 2012. Antibody-enabled small-molecule drug discovery. Nat. Rev. Drugs Discov. 11, 519–525.
Lazzeroni, L.C., Lu, Y., Belitskaya-Lévy, I., 2014. *P*-values in genomics: apparent precision masks high uncertainly. Mol. Psychiatry (In press).
Leboyer, M., Tamouza, R., Charron, D., Faucard, R., Perron, H., 2013. Human endogenous retrovirus type W (HERV-W) in schizophrenia: a new avenue of research at the gene-environment interface. World J. Psychiatry 14, 80–90.
Leclerc, E., Mansur, R.B., Brietzke, E., 2013. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J. Affect. Disord. 149, 247–252.
Lee, J.A., Chu, S., Willard, F.S., Cox, K.L., Sells Galvin, R.J., Peery, R.B., Oliver, S.E., Oler, J., Meredith, T.D., Heidler, S.A., Gough, W.H., Husain, S., Palkowitz, A.D., Moxham, C.M., 2011. Open innovation for phenotypic drug discovery: the PD2 assay panel. J. Biomol. Screen. 16, 588–602.
Lee, F.S., Heimer, H., Giedd, J.N., Lein, E.S., Sestan, N., Weinberger, D.R., Casey, B.J., 2014. Mental health. Adolescent mental health-opportunity and obligation. Science 346, 547–549.
Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., Wüst, S., Pruessner, J.C., Rietschel, M., Deuschle, M., Meyer-Lindenberg, A., 2011. City living and urban upbringing affect neural social stress processing in humans. Nature 474, 498–501.
Lehmann, H.E., Hanrahan, G.E., 1954. Chlorpromazine, new inhibiting agent for psychomotor excitement and manic states. Arch. Neurol. Psychiatry 71, 227–237.
Leifker, F.R., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2011. Validating measures of real-world outcome: the results of the VALERO expert survey and RAND panel. Schizophr. Bull. 37, 334–343.
Leonard, B.E., McCartan, D., White, J., King, D.J., 2004. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum. Psychopharmacol. Clin. Exp. 19, 151–180.
Leucht, S., 2004. Amisulpride a selective dopamine antagonist and atypical antipsychotic: results of a meta-analysis of randomized controlled trials. Int. J. Neuropsychopharmacol. 7, S15–S20.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet, 382 , 951–962 (Erratum in: Lancet 382, 940).
Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M., 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 373, 31–41.
Leucht, S., Hierl, S., Kissling, W., Dold, M., Davis, J.M., 2012. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br. J. Psychiatry 200, 97–106.
Levinson, D.F., Mostafayi, S., Milaneschi, Y., Rivera, M., Ripke, S., Wray, N.R., Sullivan, P.F., 2014. Genetic studies of major

depressive disorder: why are there no genome-wide association study findings and what can we do about it? Biol. Psychiatry 76, 510–512.
Lewis, D.A., 2012. Cortical circuit dysfunction and cognitive deficits in schizophrenia – implications for preemptive interventions. Eur. J. Neurosci. 35, 1871–1878.
Lewis, D.A., Curley, A.A., Glausier, J.R., Volk, D.W., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35, 57–67.
Lewis, R., Bagnall, A.M., Leitner, M., 2005. Sertindole for schizophrenia. Cochrane Database Syst. Rev. 20, CD001715.
Leysen, J.E., Janssen, P.M., Gommeren, W., Wynants, J., Pauwels, P.J., Janssen, P.A., 1992. In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocaperidone. Mol. Pharmacol. 41, 494–508.
Leysen, J.E., Janssen, P.M., Megens, A.A., Schotte, A., 1994. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J. Clin. Psychiatry. 55 (Suppl.), 5–12.
Li, J.W.H., Vederas, J.C., 2009. Drug discovery and natural products: end of an era or an endless frontier? Science 325, 161–165.
Lieberman, J.A., Stroup, S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S.E., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. For the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223.
Liu, J., Ogden, A., Comery, T.A., Spiros, A., Roberts, P., Geerts, H., 2014. Prediction of efficacy of Vabicaserin, a 5-HT2C agonist, for the treatment of schizophrenia using a quantitative systems pharmacology model. CPT Pharmacomet. Syst. Pharmacol. 3, e111.
Loomer, H.P., Saunders, J.C., Kline, N.S., 1958. A clinical and pharmacodynamics evaluation of iproniazid as a psychic energizer. Psychiatr. Res. Rep. 8, 129–141.
López-Muñoz, F., Alamo, C., 2009. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. Curr. Pharm. Des. 15, 1563–1586.
Löscher, W., 2002. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs 16, 669–694.
Lotufo-Neto, F., Trivedi, M., Thase, M.E., 1999. Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. Neuropsychopharmacology 20, 226–247.
Lozano, R., Hare, E.B., Hagerman, R.J., 2014. Modulation of the GABAergic pathways for the treatment of fragile X syndrome. Neuropsychiatr. Dis. Treat. 10, 1769–1779.
Lynch, D., Laws, K.R., McKenna, P.J., 2010. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychol. Med. 40, 9–24.
Maccaron, R., Banks, M.N., Bojanic, D., Burns, D.J., Cirovic, D.A., Garyantes, T., Green, D.V.S., Hertzberg, R.P., Janzen, W.P., Paslay, J.W., Schopfer, U., Sittampalam, G.S., 2011. Impact of high-throughput screening in biomedical research. Nat. Rev. Drug Discov. 10, 188–195.
McGowan, P.O., Szyf, M., 2010. The epigenetics of social adversity in early life: implications for mental health outcomes. Neurobiol. Dis. 39, 66–72.
McEwen, B.S., Chattarji, S., Diamond, D.M., Jay, T.M., Reagan, L.P., Svenningsson, P., Fuchs, E., 2010. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol. Psychiatry 15, 237–249.
Maeder, M.L., Bumcrot, D., 2014. Advancing the promise of therapeutic genomic editing. Drug Discov. World (Fall), 19–25.
Magyar, K., Szende, B., 2004. (−)-Deprenyl, a selective MAO-B inhibitor, with apoptotic and anti-apoptotic properties. Neurotoxicology 25, 233–242.
Malaspina, D., Walsh-Messinger, J., Gaebel, W., Smith, L.M., Gorun, A., Prudent, V., Antonius, D., Trémeau, F., 2014. Negative symptoms, past and present: a historical perspective and moving to DSM-5. Eur. Neuropsychopharmacol. 24, 710–724.
Manji, H., Kato, T., Di Prospero, N.A., Ness, S., Beal, M.F., Krams, M., Chen, G., 2012. Impaired mitochondrial function in psychiatric disorders. Nat. Rev. Neurosci. 13, 293–307.
Marcou, A., Chiamulera, C., Geyer, M.A., Tricklebank, M., Steckler, T., 2009. Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacology 34, 74–89.
Martin, J.L., Martín-Sánchez, E., 2012. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. Eur. Psychiatry 27, 147–155.
Martinez-Martinez, P., Molenaar, P.C., Losen, M., Stevens, J., Baets, M.H., Szoke, A., Honnorat, J., Tamouza, R., Leboyer, M., Os, J. V., Rutten, B.P., 2013. Autoantibodies to neurotransmitter receptors and ion channels: from neuromuscular to neuropsychiatric disorders. Front. Genet. 4, 181.
Maurice, P., Guillaume, J.L., Benleulmi-Chaachoua, A., Daulat, A. M., Kamal, M., Jockers, R., 2011. GPCR-interacting proteins, major players of GPCR function. Adv. Pharmacol. 62, 349–380.
Maury, Y., Gauthier, M., Peschanski, M., Martinat, C., 2011. Human pluripotent stem cells for disease modelling and drug screening. Bioessays 34, 61–71.
May, A., 2011. Experience-dependent structural plasticity in the adult human brain. Trends Cogn. Sci. 15, 475–482.
McCarthy, M.J., Welsh, D.K., 2012. Cellular circadian clocks in mood disorders. J. Biol. Rhythms 27, 339–352.
McClanahan, T.R., Donner, S.D., Maynard, J.A., MacNeil, M.A., Graham, N.A., Maina, J., Baker, A.C., Alemu, I.J.B., Beger, M., Campbell, S.J., Darling, E.S., Eakin, C.M., Heron, S.F., Jupiter, S.D., Lundquist, C.J., McLeod, E., Mumby, P.J., Paddack, M.J., Selig, E.R., van Woesik, R., 2012. Prioritizing key resilience indicators to support coral reef management in a changing climate. PLoS One 7, e42884.
McGraw, L.A., Young, L.J., 2010. The prairie vole: an emerging model organism for understanding the social brain. Trends Neurosci. 33, 103–109.
Meffre, J., Chaumont-Dubel, S., Mannoury la Cour, C., Loiseau, F., Watson, D.J., Dekeyne, A., Séveno, M., Rivet, J.M., Gaven, F., Déléris, P., Hervé, D., Fone, K.C., Bockaert, J., Millan, M.J., Marin, P., 2012. 5-HT(6) receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia. EMBO Mol. Med. 4, 1043–1045.
Mehler, M.F., 2008. Epigenetics and the nervous system. Ann. Neurol. 64, 602–617.
Mei, H., Xia, T., Feng, G., Zhu, J., Lin, S.M., Qiu, Y., 2012. Opportunities in systems biology to discover mechanisms and repurpose drugs for CNS diseases. Drug Discov. Today 17, 1208–1216.
Melander, H., Salmonson, T., Abadie, E., van Zwieten-Boot, B., 2008. A regulatory Apologia – a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur. Neuropsychopharmacol. 18, 623–627.
Mellsop, G.W., Menkes, D.B., El-Badri, S.M., 2007. Classification in psychiatry: does it deliver in schizophrenia and depression? Int. J. Ment. Health Syst. 1, 1–4.
Meltzer, H.Y., 2013. Update on typical and atypical antipsychotic drugs. Annu. Rev. Med. 64, 393–406.
Meltzer, H.Y., Alphs, L.D., Bastani, B., Ramirez, L.F., Kwon, K., 1991. Clinical efficacy of clozapine in the treatment of schizophrenia. Pharmacopsychiatry 24, 44–45.

Meltzer, H.Y., Alphs, L.D., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., Krishnan, R., Lindenmayer, J.P., Potkin, S., 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). International Suicide Prevention Trial Study Group. Arch. Gen. Psychiatry 60, 82–91.

Meltzer, H.Y., Massey, B.W., Horiguchi, M., 2012. Serotonin receptors as targets for drugs useful to treat psychosis and cognitive impairment in schizophrenia. Curr. Pharm. Biotechnol. 13, 1572–1586.

Meltzer, H.Y., Matsubara, S., Lee, J.C., 1989. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D1, D2, and serotonin2 pKi values. J. Pharmacol. Exp. Ther. 251, 238–246.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15, 483–506.

Meyer-Lindenberg, A., 2010. From maps to mechanisms through neuroimaging of schizophrenia. Nature 468, 194–202.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12, 524–538.

Micó, J.A., Ardid, D., Berrocoso, E., Eschalier, A., 2006. Antidepressants and pain. Trends Pharmacol. Sci. 27, 348–354.

Mihalopoulos, C., Vos, T., Pirkis, J., Carter, R., 2011. The economic analysis of prevention in mental health programs. Annu. Rev. Clin. Psychol. 7, 169–201.

Millan, M.J., 2000. Improving the treatment of schizophrenia: focus on serotonin (5-HT1A) receptors. J. Pharmacol. Exp. Ther. 295, 853–886.

Millan, M.J., 2002. Descending control of pain. Prog. Neurobiol. 66, 355–474.

Millan, M.J., 2003. The neurobiology and control of anxious states. Prog. Neurobiol. 70, 83–244.

Millan, M.J., 2005. Serotonin 5-HT2C receptors as a target for the treatment of depressive and anxious states: focus on novel therapeutic strategies. Therapie 60, 441–460.

Millan, M.J., 2006. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol. Ther. 110, 135–370.

Millan, M.J., 2009. Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs. Neurotherapeutics 6, 53–77.

Millan, M.J., 2013. An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. Neuropharmacology 68, 2–82.

Millan, M.J., 2014a. On 'polypharmacy' and multi-target agents, complementary strategies for improving the treatment of depression: a comparative appraisal. Int. J. Neuropsychopharmacol. 17, 1009–1037.

Millan, M.J., 2014b. The epigenetic dimension of Alzheimer's disease: causal, consequence, or curiosity? Dialogues Clin. Neurosci. 16, 373–393.

Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168.

Millan, M.J., Bales, K.L., 2013. Towards improved animal models for evaluating social cognition and its disruption in schizophrenia: the CNTRICS initiative. Neurosci. Biobehav. Rev. 37, 2166–2180.

Millan, M.J., Brocco, M., Rivet, J.M., Audinot, V., Newman-Tancredi, A., Maiofiss, L., Queriaux, S., Despaux, N., Peglion, J.L., Dekeyne, A., 2000a. S18327 (1-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)piperid-1-yl]ethyl]3-phenyl imidazolin-2-one), a novel, potential antipsychotic displaying marked antagonist properties at alpha(1)- and alpha(2)-adrenergic receptors: II. Functional profile and a multiparametric comparison with haloperidol, clozapine, and 11 other antipsychotic agents. J. Pharmacol. Exp. Ther. 292, 54–66.

Millan, M.J., Dekeyne, A., Gobert, A., Mannoury la Cour, C., Brocco, M., Rivet, J.M., Di Cara, B., Lejeune, F., Cremers, T. I., Flik, G., de Jong, T.R., Olivier, B., de Nanteuil, G., 2010. S41744, a dual neurokinin (NK)1 receptor antagonist and serotonin (5-HT) reuptake inhibitor with potential antidepressant properties: a comparison to aprepitant (MK869) and paroxetine. Eur. Neuropsychopharmacol. 20, 599–621.

Millan, M.J., Dekeyne, A., Papp, M., La Rochell, C.D., MacSweeney, C., Peglion, J.L., Brocco, M., 2001. S33005, a novel ligand at both serotonin and norepinephrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine. J. Pharmacol. Exp. Ther. 298, 581–591.

Millan, M.J., Di Cara, B., Dekeyne, A., Panayi, F., De Groote, L., Sicard, D., Cistarelli, L., Billiras, R., Gobert, A., 2007. Selective blockade of dopamine D3 vs D2 receptors enhances frontocortical cholinergic transmission and social memory in rats: a parallel neurochemical and behavioural analysis. J. Neurochem. 100, 1047–1061.

Millan, M.J., Fone, K., Steckler, T., Horan, W.P., 2014. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. Eur. Neuropsychopharmacol. 24, 645–692.

Millan, M.J., Gobert, A., Rivet, J.M., Adhumeau-Auclair, A., Cussac, D., Newman-Tancredi, A., Dekeyne, A., Nicolas, J.P., Lejeune, F., 2000b. Mirtazapine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of α2-adrenergic and serotonin2C receptors: a comparison with citalopram. Eur. J. Neurosci. 12, 1079–1095.

Millan, M.J., Goodwin, G.M., Meyer-Lindenberg, A., Ogren, S.O., 2015. 60 years of advances in neuropsychopharmacology for improving brain health: renewed hope for progress. Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2015.01.015.

Millan, M.J., Lejeune, F., Gobert, A., 2000c. Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: relevance to the actions of antidepressant agents. J. Psychopharmacol. 14, 114–138.

Mingozzi, F., High, K.A., 2011. Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges. Nat. Rev. Genet. 12, 341–355.

Minogue, K., Wolinsky, H., 2010. Lost in translation: the current focus on translating research into applications might be part of the natural cycle of research funding, but at what cost? EMBO Rep. 11, 93–96.

Mitchell, P.B., Hadzi-Pavlovic, D., 2000. Lithium treatment for bipolar disorder. Bull. World Health Organ. 78, 515–517.

Miyashiro, K.Y., Bell, T.J., Sul, J.Y., Eberwine, J., 2009. Subcellular neuropharmacology: the importance of intracellular targeting. Trends Pharmacol. Sci. 30, 203–211.

Möhler, H., 1983. Benzodiazepine receptors: mode of interaction of agonists and antagonists. Adv. Biochem. Psychopharmacol. 37, 247–254.

Möhler, H., 2012. The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology 62, 42–53.

Möhler, H., Fritschy, J.M., Rudolph, U., 2002. A new benzodiazepine pharmacology. J. Pharmacol. Exp. Ther. 300, 2–8.

Montague, P.R., Dolan, R.J., Friston, K.J., Dayan, P., 2012. Computational psychiatry. Trends Cogn Sci. 16, 72–80.

Montgomery, S.A., Baldwin, D.S., Blier, P., Fineberg, N.A., Kasper, S., Lader, M., Lam, R.W., Lépine, J.P., Möller, H.J., Nutt, D.J., Rouillon, M.E., Schatzberg, A.F., Thase, M.E., 2007. Which

antidepressants have demonstrated superior efficacy? A review of the evidence. Int. Clin. Psychopharmacol. 22, 323–329 (Review Erratum in: Int. Clin. Psychopharmacol. 2008. 23, 61).
Montgomery, S.A., Möller, H.J., 2009. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Int. Clin. Psychopharmacol. 24, 111–118.
Monti, B., Polazzi, E., Contestabile, A., 2009. Biochemical, molecular and epigenetic mechanisms of valproic acid neuroprotection. Curr. Mol. Pharmacol. 2, 95–109.
Morales, I., Guzman-Martinez, L., Cerda-Troncoso, C., Farias, G.A., Maccioni, R.B., 2014. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front. Cell. Neurosci. 8, 1–9.
Moore, N.A., Tye, N.C., Axton, M.S., Risius, F.C., 1992. The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent. J. Pharmacol. Exp. Ther. 262, 545–551.
Moreno, A.Y., Janda, K.D., 2009. Immunopharmacotherapy: vaccination strategies as a treatment for drug abuse and dependence. Pharmacol. Biochem. Behav. 92, 199–205.
Morton, W.A., Stockton, G.G., 2000. Methylphenidate abuse and psychiatric side effects. Prim Care Companion. J. Clin. Psychiatry 2, 59–164.
Mueser, K.T., Cook, J.A., 2014. Rising to the challenge of first episode psychosis: the NIMH Recovery After Initial Schizophrenia Episode (RAISE) initiative. Psychiatr. Rehabil. J. 37, 267–269.
Muglia, P., 2011. From genes to therapeutic targets for psychiatric disorders – what to expect? Curr. Opin. Pharmacol. 11 (563-57).
Mugnaini, M., Iavarone, L., Cavallini, P., Griffante, C., Oliosi, B., Savoia, C., Beaver, J., Rabiner, E.A., Micheli, F., Heidbreder, C., Andorn, A., Merlo Pich, E., Bani, M., 2012. Occupancy of brain dopamine D3 receptors and drug craving: a translational approach. Neuropsychopharmacology 38, 302–312.
Mullard, A., 2011. Could pharma open its drug freezers? Nat. Rev. Drug Discov. 10, 399–400.
Mulle, J.G., Sharp, W.G., Cubells, J.F., 2013. The gut microbiome: a new frontier in autism research. Curr. Psychiatr. Rep. 15, 337.
Müller-Schiffmann, A., März-Berberich, J., Andreyeva, A., Rönicke, R., Bartnik, D., Brener, O., Kutzsche, J., Horn, A.H., Hellmert, M., Polkowska, J., Gottmann, K., Reymann, K.G., Funke, S.A., Nagel-Steger, L., Moriscot, C., Schoehn, G., Sticht, H., Willbold, D., Schrader, T., Korth, C., 2010. Combining independent drug classes into superior, synergistically acting hybrid molecules. Angew. Chem. Int. Ed. Engl. 49, 8743–8746.
Munos, B., 2009. Lessons from 60 years of pharmaceutical innovation. Nat. Rev. Drug Discov. 8, 959–968.
Murphy, S.E., Mackay, C.E., 2010. Using MRI to measure drug action: caveats and new directions. J. Psychopharmacol. 25, 1168–1174.
Murray, R.M., Morrison, P.D., Henquet, C., Di Forti, M., 2007. Cannabis, the mind and society: the hash realities. Nat. Rev. Neurosci. 8, 885–895.
Murray C.J., Vos T., Lozano R., Naghavi M., Flaxman A.D., Michaud C., Ezzati M., Shibuya K., Salomon J.A., Abdalla S., Aboyans V., Abraham J., Ackerman I., Aggarwal R., Ahn S.Y., Ali M.K., Alvarado M., Anderson H.R., Anderson L.M., Andrews K.G., Atkinson C., Baddour L.M., Bahalim A.N., Barker-Collo S., Barrero L.H., Bartels D.H., Basáñez M.G., Baxter A., Bell M.L., Benjamin E.J., Bennett D., Bernabé E., Bhalla K., Bhandari B., Bikbov B., Bin Abdulhak A., Birbeck G., Black J.A., Blencowe H., Blore J.D., Blyth F., Bolliger I., Bonaventure A., Boufous S., Bourne R., Boussinesq M., Braithwaite T., Brayne C., Bridgett L., Brooker S., Brooks P., Brugha T.S., Bryan-Hancock C., Bucello C., Buchbinder R., Buckle G., Budke C.M., Burch M., Burney P., Burstein R., Calabria B., Campbell B., Canter C.E., Carabin H., Carapetis J., Carmona L., Cella C., Charlson F., Chen H., Cheng A.T., Chou D., Chugh S.S., Coffeng L.E., Colan S.D., Colquhoun S., Colson K.E., Condon J., Connor M.D., Cooper L.T., Corriere M., Cortinovis M., de Vaccaro K. C., Couser W., Cowie B.C., Criqui M.H., Cross M., Dabhadkar K.C., Dahiya M., Dahodwala N., Damsere-Derry J., Danaei G., Davis A., De Leo D., Degenhardt L., Dellavalle R., Delossantos A., Denenberg J., Derrett S., Des Jarlais D.C., Dharmaratne S.D., Dherani M., Diaz-Torne C., Dolk H., Dorsey E.R., Driscoll T., Duber H., Ebel B., Edmond K., Elbaz A., Ali S.E., Erskine H., Erwin P.J., Espindola P., Ewoigbokhan S.E., Farzadfar F., Feigin V., Felson D.T., Ferrari A., Ferri C.P., Fèvre E.M., Finucane M.M., Flaxman S., Flood L., Foreman K., Forouzanfar M.H., Fowkes F.G., Fransen M., Freeman M.K., Gabbe B.J., Gabriel S.E., Gakidou E., Ganatra H.A., Garcia B., Gaspari F., Gillum R.F., Gmel G., Gonzalez-Medina D., Gosselin R., Grainger R., Grant B., Groeger J., Guillemin F., Gunnell D., Gupta R., Haagsma J., Hagan H., Halasa Y.A., Hall W., Haring D., Haro J.M., Harrison J.E., Havmoeller R., Hay R.J., Higashi H., Hill C., Hoen B., Hoffman H., Hotez P.J., Hoy D., Huang J.J., Ibeanusi S.E., Jacobsen K.H., James S.L., Jarvis D., Jasrasaria R., Jayaraman S., Johns N., Jonas J.B., Karthikeyan G., Kassebaum N., Kawakami N., Keren A., Khoo J.P., King C.H., Knowlton L.M., Kobusingye O., Koranteng A., Krishnamurthi R., Laden F., Lalloo R., Laslett L.L., Lathlean T., Leasher J.L., Lee Y.Y., Leigh J., Levinson D., Lim S.S., Limb E., Lin J.K., Lipnick M., Lipshultz S.E., Liu W., Loane M., Ohno S.L., Lyons R., Mabweijano J., MacIntyre M.F., Malekzadeh R., Mallinger L., Manivannan S., Marcenes W., March L., Margolis D.J., Marks G.B., Marks R., Matsumori A., Matzopoulos R., Mayosi B.M., McAnulty J.H., McDermott M.M., McGill N., McGrath J., Medina-Mora M.E., Meltzer M., Mensah G.A., Merriman T.R., Meyer A.C., Miglioli V., Miller M., Miller T.R., Mitchell P.B., Mock C., Mocumbi A.O., Moffitt T.E., Mokdad A.A., Monasta L., Montico M., Moradi-Lakeh M., Moran A., Morawska L., Mori R., Murdoch M.E., Mwaniki M.K., Naidoo K., Nair M.N., Naldi L., Narayan K.M., Nelson P.K., Nelson R.G., Nevitt M.C., Newton C.R., Nolte S., Norman P., Norman R., O'Donnell M., O'Hanlon S., Olives C., Omer S.B., Ortblad K., Osborne R., Ozgediz D., Page A., Pahari B., Pandian J.D., Rivero A.P., Patten S.B., Pearce N., Padilla R.P., Perez-Ruiz F., Perico N., Pesudovs K., Phillips D., Phillips M.R., Pierce K., Pion S., Polanczyk G.V., Polinder S., Pope CA 3rd, Popova S., Porrini E., Pourmalek F., Prince M., Pullan R.L., Ramaiah K.D., Ranganathan D., Razavi H., Regan M., Rehm J.T., Rein D.B., Remuzzi G., Richardson K., Rivara F.P., Roberts T., Robinson C., De Leòn F.R., Ronfani L., Room R., Rosenfeld L.C., Rushton L., Sacco R.L., Saha S., Sampson U., Sanchez-Riera L., Sanman E., Schwebel D.C., Scott J.G., Segui-Gomez M., Shahraz S., Shepard D. S., Shin H., Shivakoti R., Singh D., Singh G.M., Singh J.A., Singleton J., Sleet D.A., Sliwa K., Smith E., Smith J.L., Stapelberg N.J., Steer A., Steiner T., Stolk W.A., Stovner L.J., Sudfeld C., Syed S., Tamburlini G., Tavakkoli M., Taylor H.R., Taylor J.A., Taylor W.J., Thomas B., Thomson W.M., Thurston G.D., Tleyjeh I.M., Tonelli M., Towbin J.A., Truelsen T., Tsilimbaris M.K., Ubeda C., Undurraga E. A., van der Werf M.J., van Os J., Vavilala M.S., Venketasubramanian N., Wang M., Wang W., Watt K., Weatherall D.J., Weinstock M. A., Weintraub R., Weisskopf M.G., Weissman M.M., White R.A., Whiteford H., Wiebe N., Wiersma S.T., Wilkinson J.D., Williams H. C., Williams S.R., Witt E., Wolfe F., Woolf A.D., Wulf S., Yeh P.H., Zaidi A.K., Zheng Z.J., Zonies D., Lopez A.D., AlMazroa M.A., Memish Z.A.. 2010. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197-2223.
Muscatello, M.R., Bruno, A., Micali Bellinghieri, P., Pandolfo, G., Zoccali, R.A., 2014. Sertindole in schizophrenia: efficacy and safety issues. Expert Opin. Pharmacother. 15, 1943–1953.
Muthyala, R., 2011. Orphan/rare drug discovery through drug repositioning. Drug Discov. Today Ther. Strateg. 8, 71–81.
Najjar, S., Pearlman, D.M., 2015. Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophr. Res. 161, 102–112.
Nemani, K., Hosseini Ghomi, R., McCormick, B., Fan, X., 2015. Schizophrenia and the gut-brain axis. Prog. Neuropsychopharmacol. Biol. Psychiatry 56, 155–160.

Ness, S., Rafii, M., Aisen, P., Krams, M., Silverman, W., Manji, H., 2012. Down's syndrome and Alzheimer's disease: towards secondary prevention. Nat. Rev. Drug Discov. 11, 655–656.
Neuzil, P., Giselbrecht, S., Longe, K., Huang, T.J., Manz, A., 2012. Revisiting lab-on-a-chip technology for drug discovery. Nat. Rev. Drug Discov. 11, 620–632.
Newcomer, J.W., 2005. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 19, 1–93.
Nikiforuk, A., 2014. The procognitive effects of 5-HT6 receptor ligands in animal models of schizophrenia. Rev. Neurosci. 25, 367–382.
Noack, C.H., Trautner, E.M., 1951. The lithium treatment of maniacal psychosis. Med. J. Aust. 2, 219–222.
Nomura, J., Takumi, T., 2012. Animal models of psychiatric disorders that reflect human copy number variation. Neural Plast. 2012, 589524.
Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., Brayne, C., 2014. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 13, 788–794.
Norton, W.H.J., 2013. Toward developmental models of psychiatric disorders in zebrafish. Front. Neural Circuits 7, 79.
Nussinov, R., Tsai, C.J., Csermely, P., 2011. Allo-network drugs: harnessing allostery in cellular networks. Trends Pharmacol. Sci. 32, 686–693.
Nutsford, D., Pearson, A.L., Kingham, S., 2013. An ecological study investigating the association between access to urban green space and mental health. Public Health 127, 1005–1011.
Nutt, D., 2012. Massive overuse of appropriate medical intervention? The modern-day use of antidepressants. Curr. Opin. Pharmacol. 12, 109–110.
Nutt, D., Goodwin, G., 2011. ECNP Summit on the future of CNS drug research in Europe 2011: report prepared for ECNP by David Nutt and Guy Goodwin. Eur. Neuropsychopharmacol. 21, 495–499.
Nyberg, S., Jucaite, A., Takano, A., Kågedal, M., Cselényi, Z., Halldin, C., Farde, L., 2013. Norepinephrine transporter occupancy in the human brain after oral administration of quetiapine XR. Int. J. Neuropsychopharmacol. 16, 2235–2244.
Ochodo, C., Ndetei, D.M., Moturi, W.N., Otieno, J.O., 2014. External built residential environment characteristics that affect mental health of adults. J. Urban Health 91, 908–927.
Olesen, J., Baker, M.G., Freund, T., di Luca, M., Mendlewicz, J., Ragan, I., Westphal, M., 2006. Consensus document on European brain research. J. Neurol. Neurosurg. Psychiatr. 77, i1–i49.
Olfson, M., Kroenke, K., Wang, S., Blanco, C., 2014. Trends in office-based mental health care provided by psychiatrists and primary care physicians. J. Clin. Psychiatry 75, 247–253.
Oprea, T.I., Bauman, J.E., Bologa, C.G., Buranda, T., Chigaev, A., Edwards, B.S., Jarvik, J.W., Gresham, H.D., Haynes, M.K., Hjelle, B., Hromas, R., Hudson, L., Mackenzie, D.A., Muller, C.Y., Reed, J.C., Simons, P.C., Smagley, Y., Strouse, J., Surviladze, Z., Thompson, T., Ursu, O., Waller, A., Wandinger-Ness, A., Winter, S.S., Wu, Y., Young, S.M., Larson, R.S., Willman, C., Sklar, L.A., 2011. Drug repurposing from an academic perspective. Drug Discov. Today Ther. Strateg. 8, 61–69.
Owen, R.T., 2006. Ramelteon: profile of a new sleep-promoting medication. Drugs Today 42, 255–263.
Owen, R.T., 2007. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. Drugs Today 43, 601–610.
Page, M.E., Cryan, J.F., Sullivan, A., Dalvi, A., Saucy, B., Manning, D.R., Lucki, I., 2002. Behavioral and neurochemical effects of 5-(4-[4-(5-Cyano-3-indolyl)-butyl)-butyl]-1-piperazinyl)-benzofuran-2-carboxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine(1A) receptor partial agonist. J. Pharmacol. Exp. Ther. 302, 1220–1227.
Pammolli, F., Magazzini, L., Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. Nat. Rev. Drug Discov. 10, 428–438.
Pande, A.C., Crockatt, J.G., Feltner, D.E., Janney, C.A., Smith, W. T., Weisler, R., Londborg, P.D., Bielski, R.J., Zimbroff, D.L., Davidson, J.R., Liu-Dumaw, M., 2003. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am. J. Psychiatry 160, 533–540.
Panksepp, J., 2010. Affective neuroscience of the emotional brain mind: evolutionary perspectives and implications for understanding depression. Dialogues Clin. Neurosci. 12, 533–545.
Panizzon, L., 1944. La preparazione di piridile piridilarilac - tonitrilie di alcuni prodotti transformazione (part la). Helv. Chim. Acta 2, 1748–1756.
Papakostas, G.J., Nelson, J.C., Kasper, S., Moller, H.J., 2008. A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. Eur. Neuropsychopharmacol. 18, 122–127.
Papaleo, F., Lipska, B.K., Weinberger, D.R., 2012. Mouse models of genetic effects on cognition: relevance to schizophrenia. Neuropharmacology 62, 1204–1220.
Pardridge, W.M., 2007. shRNA and siRNA delivery to the brain. Adv. Drug Deliv. Rev. 59, 141–152.
Parmentier, H., Garcia-Campayo, J., Prieto, R., 2013. Comprehensive review of generalized anxiety disorder in primary care in Europe. Curr. Med. Res. Opin. 29, 355–367.
Patel, A., Knapp, M., Romeo, R., Reeder, C., Matthiasson, P., Everitt, B., Wykes, T., 2010. Cognitive remediation therapy in schiozophrenia: cost-effectiveness analysis. Schizophr. Res. 20, 217–224.
Penn, D.L., Roberts, D.L., Combs, D., Sterne, A., 2007. Best practices: the development of the social cognition and interaction training program for schizophrenia spectrum disorders. Psychiatr. Serv. 58, 449–451.
Penrod, N.M., Cowper-Sal-lari, R., Moore, J.H., 2011. Systems genetics for drug target discovery. Trends Pharmacol. Sci. 32, 623–630.
Perez-Rodriguez, M., Mahon, K., Russo, M., Ungar, A.K., Burdick, K. E., 2014. Eur Neuropsychopharmacol., in press. HYPERLINK "/pubmed/25153535"Oxytocin and social cognition in affective and psychotic disorders. http://dx.doi.org/10.1016/j.euroneuro.2014.07.012.
Perron, H., Hamdani, N., Faucard, R., Lajnef, M., Jamain, S., Daban-Huard, C., Sarrazin, S., LeGuen, E., Houenou, J., Delavest, M., Moins-Teisserenc, H., Bengoufa, D., Yolken, R., Madeira, A., Garcia-Montojo, M., Gehin, N., Burgelin, I., Ollagnier, G., Bernard, C., Dumaine, A., Henrion, A., Gombert, A., Le Dudal, K., Charron, D., Krishnamoorthy, R., Tamouza, R., Leboyer, M., 2012. Molecular characteristics of Human Endogenous Retrovirus type-W in schizophrenia and bipolar disorder. Transl. Psychiatry 2, e201.
Pertea, M., Salzberg, S.L., 2010. Between a chicken and a grape; estimating the number of human genes. Genome Biol. 11 (5), 206. http://dx.doi.org/10.1186/gb-2010-11-5-206.
Phillips, J., Frances, A., Cerullo, M.A., Chardavoyne, J., Decker, H. S., First, M.B., Ghaemi, N., Greenberg, G., Hinderliter, A.C., Kinghorn, W.A., LoBello, S.G., Martin, E.B., Mishara, A.L., Paris, J., Pierre, J.M., Pies, R.W., Pincus, H.A., Porter, D., Pouncey, C., Schwartz, M.A., Szasz, T., Wakefield, J.C., Waterman, G.S., Whooley, O., Zachar, P., 2012. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: General conclusion. Philos. Ethics Humanit. Med. 7, 1–14.
Pilc, A., Wierońska, J.M., Skolnick, P., 2013. Glutamate-based antidepressants: preclinical psychopharmacology. Biol. Psychiatry 73, 1125–1132.
Pilla Reddy, V., Kozielska, M., Johnson, M., Suleiman, A.A., Vermeulen, A., Liu, J., de Greef, R., Groothuis, G.M., Danhof, M., Proost, J.H., 2012. Modelling and simulation of the Positive and Negative Syndrome Scale (PANSS) time course and dropout

hazard in placebo arms of schizophrenia clinical trials. Clin. Pharmacokinet. 51, 261–275.
Pizarro, M., Fontenelle, L.F., Paravidino, D.C., Yücel, M., Miguel, E. C., de Menezes, G.B., 2014. An updated review of antidepressants with marked serotonergic effects in obsessive-compulsive disorder. Expert Opin. Pharmacother. 15, 1391–1401.
Pletscher, A., Shore, P.A., Brodie, B.B., 1956. Serotonin as a mediator of reserpine action in brain. J. Pharmacol. Exp. Ther. 116, 84–89.
Plichta, M.M., Schwarz, A.J., Grimm, O., Morgen, K., Mier, D., Haddad, L., Meyer-Lindenberg, A., 2012. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. Neuroimage 60, 1746–1758.
Poels, E.M., Kegeles, L.S., Kantrowitz, J.T., Slifstein, M., Javitt, D. C., Lieberman, J.A., Abi-Dargham, A., Girgis, R.R., 2014. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. Mol. Psychiatry 19, 20–29.
Pomarol-Clotet, E., Honey, G.D., Murray, G.K., Corlett, P.R., Absalom, A.R., Lee, M., McKenna, P.J., Bullmore, E.T., Fletcher, P.C., 2006. Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br. J. Psychiatry 189, 173–191.
Pop, A.S., Gomez-Mancilla, B., Neri, G., Willemsen, R., Gasparini, F., 2014. Fragile X syndrome: a preclinical review on metabotropic glutamate receptor 5 (mGluR5) antagonists and drug development. Psychopharmacology 231, 1217–1226.
Powell, C.M., Miyakawa, T., 2006. Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? Biol. Psychiatry 59, 1198–1207.
Pratt, J., Winchester, C., Dawson, N., Morris, B., 2012. Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap. Nat. Rev. Drug Discov. 11, 560–579.
Priest, R.G., Gimbrett, R., Roberts, M., Steinert, J., 1995. Reversible and selective inhibitors of monoamine oxidase A in mental and other disorders. Acta Psychiatr. Scand. 386, 40–43.
Prinz, F., Schlange, T., Asadullah, K., 2011. Believe it or not: how much can we rely on published data on potential drug targets? Nat. Rev. Drug Discov. 10, 712.
Purcell, S.M., Moran, J.L., Fromer, M., Ruderfer, D., Solovieff, N., Roussos, P., O'Dushlaine, C., Chambert, K., Bergen, S.E., Kähler, A., Duncan, L., Stahl, E., Genovese, G., Fernández, E., Collins, M.O., Komiyama, N.H., Choudhary, J.S., Magnusson, P.K., Banks, E., Shakir, K., Garimella, K., Fennell, T., DePristo, M., Grant, S. G., Haggarty, S.J., Gabriel, S., Scolnick, E.M., Lander, E.S., Hultman, C.M., Sullivan, P.F., McCarroll, S.A., Sklar, P., 2014. A polygenic burden of rare disruptive mutations in schizophrenia. Nature 506, 185–189.
Qiao, X., Sun, G., Clare, J.J., Werkman, T.R., Wadman, W.J., 2014. Properties of human brain sodium channel α-subunits expressed in HEK293 cells and their modulation by carbamazepine, phenytoin and lamotrigine. Br. J. Pharmacol. 171, 1054–1067.
Rabipour, S., Raz, A., 2012. Training the brain: fact and fad in cognitive and behavioral remediation. Brain Cogn. 79, 159–179.
Randall, L.O., 1961. Pharmacology of chlordiazepoxide ('Librium'). Dis. Nerv. Syst. 22, 7–15.
Rapoport, J.L., 2013. Pediatric psychopharmacology: too much or too little? World Psychiatry 12, 118–123.
Rapoport, S.I., Basselin, M., Kim, H.W., Rao, J.S., 2009. Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res. Rev. 61, 185–209.
Rask-Andersen, M., Almën, M.S., Schiöth, H.B., 2011. Trends in the exploitation of novel drug targets. Nat. Rev. Drug Discov. 10, 579–590.
Ratti, E., Bellew, K., Bettica, P., Bryson, H., Zamuner, S., Archer, G., Squassante, L., Bye, A., Trist, D., Krishnan, K.R., Fernandes, S., 2011. Results from 2 randomized, double-blind, placebo-controlled studies of the novel NK1 receptor antagonist casopitant in patients with major depressive disorder. J. Clin. Psychopharmacol. 31, 727–733.
Réale, D., Reader, S.M., Sol, D., McDougall, P.T., Dingemanse, N.J., 2007. Integrating animal temperament within ecology and evolution. Biol. Rev. 82, 291–318.
Reardon, S., 2014. NIH rethinks psychiatry trials. Nature 507, 288.
Reaume, A.G., 2011. Drug repurposing through non-hypothesis driven phenotypic screening. Drug Discov. Today Ther. Strategy 8, 85.
Rees, E., Kirov, G., Sanders, A., Walters, J.T., Chambert, K.D., Shi, J., Szatkiewicz, J., O'Dushlaine, C., Richards, A.L., Green, E.K., Jones, I., Davies, G., Legge, S.E., Moran, J.L., Pato, C., Pato, M., Genovese, G., Levinson, D., Duan, J., Moy, W., Göring, H.H., Morris, D., Cormican, P., Kendler, K.S., O'Neill, F.A., Riley, B., Gill, M., Corvin, A., Wellcome Trust Case Control Consortium, Craddock, N., Sklar, P., Hultman, C., Sullivan, P.F., Gejman, P.V., McCarroll, S.A., O'Donovan, M.C., Owen, M.J., 2014. Evidence that duplications of 22q11.2 protect against schizophrenia. Mol. Psychiatry 19, 37–40.
Regier, D.A., Kuhl, E.A., Kupfer, D.J., 2013. The DSM-5: classification and criteria changes. World Psychiatry 12, 92–98.
Reichelt, A.C., Rodgers, R.J., Clapcote, S.J., 2012. The role of neurexins in schizophrenia and autistic spectrum disorder. Neuropharmacology 62, 1519–1526.
Ren, Y., Wang, H., Xiao, L., 2013. Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia. Int. J. Neuropsychopharmacol. 16, 691–700.
Réus, G.Z., Dos Santos, M.A., Abelaira, H.M., Quevedo, J., 2014. Animal models of social anxiety disorder and their validity criteria. Life Sci. 114, 1–3.
Révy, D., Jaouen, F., Salin, P., Melon, C., Chabbert, D., Tafi, E., Concetta, L., Langa, F., Amalric, M., Kerkerian-Le Goff, L., Marie, H., Beurrier, C., 2014. Cellular and behavioral outcomes of dorsal striatonigral neuron ablation: new insights into striatal functions. Neuropsychopharmacology 39, 2662–2672.
Richards, T., Montori, V.M., Godlee, F., Lapsley, P., Paul, D., 2013. Let the patient revolution begin. British Medical Journal, May 14;346:f2614. http://dx.doi.org/10.1136/bmj.f2614.
Richardson, E.A., Pearce, J., Mitchell, R., Kingham, S., 2013. Role of physical activity in the relationship between urban green space and health. Public Health 127, 318–324.
Rickels, K., Clark, T.W., Ewing, J.H., Klingensmith, W.C., Morris, H. M., Smock, C.D., 1959. Evaluation of tranquilizing drugs in medical outpatients. J. Am. Med. Assoc. 171, 1649–1656.
Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Multicenter Genetic Studies of Schizophrenia Consortium, Levinson, D.F., Gejman, P.V., Kendler, K.S., Laurent, C., Mowry, B.J., O'Donovan, M.C., Owen, M.J., Pulver, A.E., Riley, B.P., Schwab, S.G., Wildenauer, D.B., Dudbridge, F., Holmans, P., Shi, J., Albus, M., Alexander, M., Campion, D., Cohen, D., Dikeos, D., Duan, J., Eichhammer, P., Godard, S., Hansen, M., Lerer, F.B., Liang, K.Y., Maier, W., Mallet, J., Nertney, D.A., Nestadt, G., Norton, N., O'Neill, F.A., Papadimitriou, G.N., Ribble, R., Sanders, A.R., Silverman, J.M., Walsh, D., Williams, N.M., Wormley, B., Psychosis Endophenotypes International Consortium, Arranz, M.J., Bakker, S., Bender, S., Bramon, E., Collier, D., Crespo-Facorro, B., Hall, J., Iyegbe, C., Jablensky, A., Kahn, R.S., Kalaydjieva, L., Lawrie, S., Lewis, C.M., Lin, K., Linszen, D.H., Mata, I.,

McIntosh, J., Murray, R.M., Ophoff, R.A., Powell, J., Rujescu, D., Van Os, J., Walshe, M., Weisbrod, M., Wiersma, D., Wellcome Trust Case Control Consortium 2, Donnelly, P., Barroso, I., Blackwell, J.M., Bramon, E., Brown, M.A., Casas, J.P., Corvin, A.P., Deloukas, P., Duncanson, A., Jankowski, J., Markus, H.S., Mathew, C.G., Palmer, C.N., Plomin, R., Rautanen, A., Sawcer, S.J., Trembath, R.C., Viswanathan, A.C., Wood, N.W., Spencer, C.C., Band, G., Bellenguez, C., Freeman, C., Hellenthal, G., Giannoulatou, E., Pirinen, M., Pearson, R.D., Strange, A., Su, Z., Vukcevic, D., Donnelly, P., Langford, C., Hunt, S.E., Edkins, S., Gwilliam, R., Blackburn, H., Bumpstead, S.J., Dronov, S., Gillman, M., Gray, E., Hammond, N., Jayakumar, A., McCann, O.T., Liddle, J., Potter, S.C., Ravindrarajah, R., Ricketts, M., Tashakkori-Ghanbaria, A., Waller, M.J., Weston, P., Widaa, S., Whittaker, P., Barroso, I., Deloukas, P., Mathew, C.G., Blackwell, J.M., Brown, M.A., Corvin, A.P., McCarthy, M.I., Spencer, C.C., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C. M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45, 1150–1159.

Risacher, S.L., Saykin, A.J., 2013. Neuroimaging and other biomarkers for Alzheimer's disease: the changing landscape of early detection. Annu. Rev. Clin. Psychol. 9, 621–648.

Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., Cabeza, R., 2011. Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. J. Psychiatr. Res. 45, 577–587.

Robbins, T.W., Gillan, C.M., Smith, D.G., de Wit, S., Ersche, K.D., 2012. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn. Sci. 16, 81–91.

Robinson, J.G., Hodges, E.A., Davison, J., 2014. Prostate-specific antigen screening: a critical review of current research and guidelines. J. Am. Assoc. Nurse Pract. 26, 574–581.

Rocca, P., Montemagni, C., Zappia, S., Piera, R., Sigaudo, M., Bogetto, F., 2014. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. Psychiatr. Res. 218, 284–289.

Roff, G., Mumby, P.J., 2012. Global disparity in the resilience of coral reefs. Trends Ecol. Evol. 27, 404–413.

Rosa, G.M., Carbone, F., Parodi, A., Massimelli, E.A., Brunelli, C., Mach, F., Vuilleumier, N., Montecucco, F., 2014. Update on the efficacy of statin treatment in acute coronary syndrome. Eur. J. Clin. Invest. 44, 501–515.

Ross, S.B., Renyi, A.L., 1967. Inhibition of the uptake of tritiated catecholamines by antidepressant and related agents. Eur. J. Pharmacol. 2, 181–186.

Roth, B.L., Craigo, S.C., Choudhary, M.S., Uluer, A., Monsma Jr, F. J., Shen, Y., Meltzer, H.Y., Sibley, D.R., 1994. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. J. Pharmacol. Exp. Ther. 268, 1403–1410.

Rotondi, A.J., Anderson, C.M., Haas, G.L., Eack, S.M., Spring, M.B., Ganguli, R., Newhill, C., Rosenstock, J., 2010. Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. Psychiatr. Serv. 61, 1099–1105.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., et al., 2006. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N. Engl. J. Med. 354, 1231–1242.

Sabbag, R., Levin, R., Edelman, S., Heresco-Levy, U., 2011. Preventive pharmacological treatment – an evolving new concept in schizophrenia. Isr. J. Psychiatr. Relat. Sci. 48, 82–90.

Sacks, S., Fisher, M., Garrett, C., Alexander, P., Holland, C., Rose, D., Hooker, C., Vinogradov, S., 2013. Combining computerized social cognitive training with neuroplasticity-based auditory training in schizophrenia. Clin. Schizophr. Relat. Psychoses 7, 78-86A.

Salinas, S., Schiavo, G., Kremer, E.J., 2010a. A hitchhiker's guide to the nervous system: the complex journey of viruses and toxins. Nat. Rev. Microbiol. 8, 645–655.

Sallee, F., Connor, D.F., Newcorn, J.H., 2013. A review of the rationale and clinical utilization of α2-adrenoceptor agonists for the treatment of attention-deficit/hyperactivity and related disorders. J. Child Adolesc. Psychopharmacol. 23, 308–319.

Sams-Dodd, F., 2013. Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift. Drug Discov. Today 18, 211–217.

Samwald, M., Adlassnig, K.P., 2013. Pharmacogenomics in the pocket of every patient? A prototype based on quick response codes. J. Am. Med. Inform Assoc. 20, 409–412.

Sanchez, C., Asin, K.E., Artigas, F., 2015. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol. Ther. 145, 45–57.

Sanford, M., 2013. Lurasidone: in the treatment of schizophrenia. CNS Drugs 27, 67–80.

Sanger, D.J., 2004. The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. CNS Drugs 18, 9–15.

Sargant, W., Dally, P., 1962. Treatment of anxiety states by antidepressant drugs. Br. Med. J. 1, 322–332.

Sarris, J., Panossian, A., Schweitzer, I., Stough, C., Scholey, A., 2011. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. Eur. Neuropsychopharmacol. 21, 841–860.

Scarr, E., Millan, M.J., Bahn, S., Bertolino, A., Turck, C.W., Insel, T. R., Kapur, S., Javitt, D.C., Moller, H.-J., Dean, B., 2015. Biomarkers for psychiatry: the journey from fantasy to fact, a report of the 2013 CINP think-tank. Int. J. Neuropsychopharmacol. (in press).

Scattoni, M.L., Crawley, J., Ricceri, L., 2009. Ultrasonic vocalizations: a tool for behavioural phenotyping of mouse models of neurodevelopmental disorders. Neurosci. Biobehav. Rev. 33, 508–515.

Schennach, R., Musil, R., Möller, H.J., Riedel, M., 2012. Functional outcomes in schizophrenia: employment status as a metric of treatment outcome. Curr. Psychiatr. Rep. 14, 229–236.

Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am. J. Psychiatry 122, 509–522.

Schindler, W., Häfliger, F., 1954. Über Derivate des Iminobenzyls. Helvet. Chim. Acta 37, 472–483.

Schultz-Kirkegaard, H., Valentin, F., 2014. Academic drug discovery centres: the economic and organisational sustainability of an emerging model. Drug Discov. Today 19, 1699–1710.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–426.

Schlaepfer, T.E., Agren, H., Monteleone, P., Gasto, C., Pitchot, W., Rouillon, F., Nutt, D.J., Kasper, S., 2012. The hidden third: improving outcome in treatment-resistant depression. J. Psychopharmacol. 26, 587–602.

Schlaepfer, T.E., Bewernick, B.H., 2013. Deep brain stimulation for major depression. Handb. Clin. Neurol. 116, 235–243.

Schmid, B., Haass, C., 2013. Genomic editing opens new avenues for zebrafish as a model for neurodegeneration. J. Neurochem. 127, 461–470.

Schneider, G., 2010. Virtual screening; an endless staircase? Nat. Rev. Drug Discov. 9, 273–276.

Schotte, A., Janssen, P.F., Gommeren, W., Luyten, W.H., Van Gompel, P., Lesage, A.,S., De Loore, K., Leysen, J.E., 1996. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology 124, 57–73.

Schou, M., Juel-Nielsen, N., Stromgren, E., Voldby, H., 1954. The treatment of manic psychoses by the administration of lithium salts. J. Neurol. Neurosurg. Psychiatry 17, 250–260.
Schughart, K., Libert, C., SYSGENET Consortium, Kas, M.J., 2013. Controlling complexity: the clinical relevance of mouse complex genetics. Eur. J. Hum. Genet. 21, 1191–1196.
Schumann, G., Binder, E.B., Holte, A., de Kloet, E.R., Oedegaard, K.J., Robbins, T.W., Walker-Tilley, T.R., Bitter, I., Brown, V.J., Buitelaar, J., Ciccocioppo, R., Cools, R., Escera, C., Fleischhacker, W., Flor, H., Frith, C.D., Heinz, A., Johnsen, E., Kirschbaum, C., Klingberg, T., Lesch, K.P., Lewis, S., Maier, W., Mann, K., Martinot, J.L., Meyer-Lindenberg, A., Müller, C.P., Müller, W.E., Nutt, D.J., Persico, A., Perugi, G., Pessiglione, M., Preuss, U.W., Roiser, J.P., Rossini, P.M., Rybakowski, J.K., Sandi, C., Stephan, K.E., Undurraga, J., Vieta, E., van der Wee, N., Wykes, T., Haro, J.M., Wittchen, H.U., 2014. Stratified medicine for mental disorders. Eur. Psychopharmacol., 24; , 5–50.
Schwarz, A.J., Becerra, L., Upadhyay, J., Anderson, J., Baumgartner, R., Coimbra, A., Evelhoch, J., Hargreaves, R., Robertson, B., Iyengar, S., Tauscher, J., Bleakman, D., Borsook, D., 2011. A procedural framework for good imaging practice in pharmacological fMRI studies applied to drug development 2: protocol optimization and best practices. Drug Discov. Today 16, 583–593.
Schwarz, A.J., Gass, N., Sartorius, A., Risterucci, C., Spedding, M., Schenker, E., Weber-Fahr, W., 2013. Anti-correlated cortical networks of intrinsic connectivity in the rat brain. Brain Connect. 3, 503–511.
Seeger, T.F., Seymour, P.A., Schmidt, A.W., Schulz, D.W., Lebel, L. A., McLean, S., Guanowsky, V., Howard, H.R., Lowe 3rd, J.A., et al., 1995. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J. Pharmacol. Exp.Therap. 275 (1), 101–113.
Seeman, P., Lee, T., Chau-Wong, M., Wong, K., 1976. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261, 717–719.
Seeman, P., Chau-Wong, M., Tedesco, J., Wong, K., 1975. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc. Natl. Acad. Sci. USA 72, 4376–4380.
Ségalat, L., 2010. System crash (Science and finance: same symptoms, same dangers?). EMBO Rep. 11, 86–89.
Selle, V., Schalkwijk, S., Vázquez, G.H., Baldessarini, R.J., 2014. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry 47, 43–52.
Shapiro, D.A., Renock, S., Arrington, E., Chiodo, L.A., Liu, L.X., Sibley, D.R., Roth, B.L., Mailman, R., 2003. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 28, 1400–1411.
Sharan, P., Gallo, C., Gureje, O., Lamberte, E., Mari, J.J., Mazzotti, G., Patel, V., Swartz, L., Olifson, S., Levav, I., de Francisco, A., Saxena, S., World Health Organization-Global Forum for Health Research – Mental Health Research Mapping Project Group, 2009. Mental health research priorities in low- and middle-income countries of Africa, Asia, Latin America and the Caribbean. Br. J. Psychiatry 195, 354–363.
Shelton, R.C., Miller, A.H., 2010. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Prog. Neurobiol. 91, 275–299.
Shen, J., et al., 2011. A 6-week randomized, double-blind, placebo-controlled, comparator-referenced, multicentre trial of vabicaserin in subjects with acute exacerbation of schizophrenia. Neuropsychopharmacology 36, S106.
Shiovitz, T.M., Wilcox, C.S., Gevorgyan, L., Shawkat, A., 2013. CNS sites cooperate to detect duplicate subjects with a clinical trial subject registry. Innov. Clin. Neurosci. 10, 17–21.
Sierksma, A.S.R., van den Hove, D.L.A., Steinbusch, H., Prickaerts, J., W.M., 2010. Major depression cognitive dysfunction and Alzheimer's disease: is there a link? Eur. J. Pharmacol. 626, 72–82.
Sigurdsson, T., Stark, K.L., Karayiorgou, M., Gogos, J.A., Gordon, J. A., 2010. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature 464, 763–767.
Silverman, E.K., Loscalzo, J., 2012. Network medicine approaches to the genetics of complex diseases. Discov. Med. 2012 (14), 143–152.
Simmons, J.M., Quinn, K.J., 2014. The NIMH research domain criteria (DRoC) project: implications for genetics research. Mamm. Genome 25, 23–31.
Skolnick, P., Basile, A.S., 2006. Triple reuptake inhibitors as antidepressants. Drug Discov. Today Ther. Strat. 3, 489–494.
Spillantini, M.G., Goedert, M., 2013. Tau pathology and neurodegeneration. Lancet Neurol. 12, 609–622.
Skripka-Serry, J., 2013. The great neuro-pipeline brain drain (and why big pharma hasn't given up on CNS disorders). Drug Discov. World (Fall), 9–17.
Slusher, B.S., Conn, P.J., Frye, S., Glicksman, M., Arkin, M., 2013. Bringing together the academic drug discovery community. Nat. Rev. Drug Discov. 12, 811–812.
Smiałowska, M., Szewczyk, B., Woźniak, M., Wawrzak-Wleciał, A., Domin, H., 2013. Glial degeneration as a model of depression. Pharmacol. Rep. 65, 1572–1579.
Smith, R.B., 2011. Repositioned drugs: integrating intellectual property and regulatory strategies. Drug Discov. Today: Ther. Strategy 8, 131.
Sodhi, A., Montaner, S., Gutkind, J.S., 2004. Viral hijacking of G-protein-coupled-receptor signalling networks. Nat. Rev. Mol. Cell Biol. 5, 998–1012.
Sokolowski, M.B., 2010. Social interactions in “simple” model systems. Neuron 65, 780–794.
Salinas, S., Schiavo, G., Kremer, E.J., 2010b. A hitchhiker's guide to the nervous system: the complex journey of viruses and toxins. Nat. Rev. Microbiol. 8, 645–655.
Smits, J.A., Rosenfield, D., Otto, M.W., Marques, L., Davis, M.L., Meuret, A.E., Simon, N.M., Pollack, M.H., Hofmann, S.G., 2013. D-cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions. J. Psychiatr. Res. 47 (1455-1446).
Spalding, K.L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H.B., Boström, E., Westerlund, I., Vial, C., Buchholz, B.A., Possnert, G., Mash, D.C., Druid, H., Frisen, J., 2013. Dynamics of hippocampal neurogenesis in adult humans. Cell 153, 1219–1227.
Stark, P., Hardison, C.D., 1985. A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. J. Clin. Psychiatry 46, 53–58.
Statucka, M., Walder, D.J., 2013. Efficacy of social cognition remediation programs targeting facial affect recognition deficits in schizophrenia: a review and consideration of high-risk samples and sex differences. Psychiatr. Res. 206, 125–139.
Steckler, T., 2015. Editorial: Preclinical data reproducibility for R&D – the challenge for neuroscience. Psychopharmacology 237, 317–320.
Stein, D.J., 2013. What is a mental disorder? A perspective from cognitive-affective science. Can. J. Psychiatry 58, 656–662.
Stein, D.J., Picarel-Blanchot, F., Kennedy, S.H., 2013. Efficacy of the novel antidepressant agomelatine for anxiety symptoms in major depression. Hum. Psychopharmacol. 28, 151–159.
Sternbach, L.H., 1983. The benzodiazepine story. J. Psychoact. Drugs 15, 15–17.
Stoyanova-Beninska, V.V., Wohlfarth, T., Isaac, M., Kalverdijk, L.J., van den Berg, H., Gispen-de Wied, C., 2011. The EU paediatric regulation: effects on paediatric psychopharmacology in Europe. Eur. Neuropsychopharmacol. 21, 565–570.

Strawn, J.R., Geracioti, T.D., 2007. The treatment of generalized anxiety disorder with pregabalin, an atypical anxiolytic. Neuropsychiatr. Dis. Treat. 3, 237–243.
Strohl, M.P., 2011. Bradley's Benzedrine studies on children with behavioral disorders. Yale J. Biol. Med. 84, 27–33.
Subramaniam, K., Luks, T.L., Fisher, M., Simpson, G.V., Nagarajan, S., Vinogradov, S., 2012. Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 73, 842–853.
Südhof, T.C., 2012. The presynaptic active zone. Neuron 75, 11–25.
Suhy, D., 2014. In it for the long haul: vector mediated therapeutics based upon DNA-directed RNA interference. Drug Discov. World (Fall), 22–29.
Svenningsson, P., Fuchs, E., 2010. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol. Psychiatry 15, 237–249.
Swerdlow, N.R., 2012. Beyond antipsychotics: pharmacologically-augmented cognitive therapies (PACTs) for schizophrenia. Neuropsychopharmacology 37, 310–311.
Swinney, D.C., 2014. Opportunities for phenotypic screening in drug discovery. Drug Discov. World (Fall), 33–40.
Swinney, D.C., Anthony, J., 2011. How were new medicines discovered? Nat. Rev. Drug Discov. 10, 507–519.
Szyf, M., 2015. Epigenetics, a key for unlocking complex CNS disorders? Therapeutic implications. Eur. Neuropsychopharmacol. this issue, http://dx.doi.org/10.1016/j.euroneuro.2014.01.009.
Szyf, M., Bick, J., 2013. DNA methylation: a mechanism for embedding early life experiences in the genome. Child Dev. 84, 49–57.
Tabares-Seisdedos, R., Rubenstein, J.L., 2013. Inverse cancer comorbidity: a serendipitous opportunity to gain insight into CNS disorders. Nat. Rev. Neurosci. 14, 293–304.
Talpos, J., Steckler, T., 2013. Touching on translation. Cell Tissue Res. 354, 297–308.
Tansey, K.E., Guipponi, M., Perroud, N., Bondolfi, G., Domenici, E., Evans, D., Hall, S.K., Hauser, J., Henigsberg, N., Hu, X., Jerman, B., Maier, W., Mors, O., O'Donovan, M., Peters, T.J., Placentino, A., Rietschel, M., Souery, D., Aitchison, K.J., Craig, I., Farmer, A., Wendland, J.R., Malafosse, A., Holmans, P., Lewis, G., Lewis, C.M., Stensbøl, T.B., Kapur, S., McGuffin, P., Uher, R., 2012. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. PLoS One 9, e1001326.
Tarazi, F.I., Riva, M.A., 2013. The preclinical profile of lurasidone: clinical relevance for the treatment of schizophrenia. Expert Opin. Drug Discov. 8, 1297–1307.
Taylor, D., Sparshatt, A., Varma, S., Olofinjana, O., 2014. Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies. Br. Med. J. 348, g1888.
Terstappen, G.C., Schlüpen, C., Raggiaschi, R., Gaviraghi, G., 2007. Target deconvolution strategies in drug discovery. Nat. Rev. Drug Discov. 6, 891–903.
Thase, M.E., Macfadden, W., Weisler, R.H., Chang, W., Paulsson, B., Khan, A., Calabrese, J.R., 2006. Efficacy of quetiapine monotherapy in bipolar I and II depression. J. Clin. Psychopharmacol. 26, 600–609.
Tobin, J.M., Bird, I.F., Boyle, D.E., 1960. Preliminary evaluation of Librium (Ro5-0690) in the treatment of anxiety reactions. Dis. Nerv. Syst. 21, 11–19.
Tomlinson, M., Rudan, I., Saxena, S., Swartz, L., Tsai, A.C., Patel, V., 2009. Setting priorities for global mental health research. Bull. World Health Organ. 87, 438–446.
Toth, C., 2014. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. Ther. Adv. Drug Saf. 5, 38–56.
Tran, P., Skolnick, P., Czobor, P., Huang, N.Y., Bradshaw, M., Mckinney, A., Fava, M., 2012. Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. J. Psychiatr. Res. 46, 64–71.
Uher, R., 2011. Genes, environment, and individual differences in responding to treatment for depression. Harv. Rev. Psychiatry 19, 109–134.
Vaccarino, F.M., Stevens, H.E., Kocabas, A., Palejev, D., Szekely, A., Grigorenko, E.L., Weissman, S., 2011. Induced pluripotent stem cells: a new tool to confront the challenge of neuropsychiatric disorders. Neuropharmacology 60, 1355–1363.
Van Alphen, B., van Swinderen, B., 2013. Drosophila strategies to study psychiatric disorders. Brain Res. Bull. 92, 1–11.
Van Coevorden-Hameete, M.H., de Graaff, E., Titulaer, M.J., Hoogenraad, C.C., Sillevis Smitt, P.A.E., 2014. Molecular and cellular mechanisms underlying anti-neuronal antibody mediated disorders of the central nervous system. Autoimmun. Rev. 13, 299–312.
Van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychol. Rev. 24, 32–48.
Van der Feltz-Cornelis, C.M., van Os, J., Knappe, S., Schumann, G., Vieta, E., Wittchen, H.U., Lewis, S.W., Elfeddali, I., Wahlbeck, K., Linszen, D., Obradors-Tarragó, C., Haro, J.M., 2014. Towards Horizon 2020: challenges and advances for clinical mental health research – outcome of an expert survey. Neuropsychiatr. Dis. Treat. 10, 1057–1068.
Van Rossum, J.M., 1966. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. Arch. Int. Pharmacodyn. Ther. 160, 492–494.
Van Megen, H.J., Westenberg, H.G., den Boer, J.A., Kahn, R.S., 1996. Cholecystokinin in anxiety. Eur. Neuropsychopharmacol. 6, 263–280.
Van Riet-Nales, D.A., Römkens, E.G., Saint-Raymond, A., Kozarewicz, P., Schobben, A.F., Egberts, T.C., Rademaker, C.M., 2014. Oral medicines for children in the European paediatric investigation plans. PLoS One 4, e98348.
Van Praag, H., 2009. Exercise and the brain: something to chew on. Trends Neurosci. 32, 283–290.
Varga, S., 2011. Defining mental disorder. Exploring the natural function approach. 2011. Philos. Ethics Humanit. Med. 6, 1.
Veenstra-VanderWeele, J., Warren, Z., 2015. Intervention in the context of development: pathways toward new treatments. Neuropsychopharmacology 40, 225–237.
Verheij, M.M.M., Cools, A.R., 2008. Twenty of dopamine research: individual differences in the response of accumbal dopamine to environmental and pharmacological challenges. Eur. J. Pharmacol. 585, 228–244.
Vieta, E., Valentí, M., 2013. Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. CNS Drugs 27, 515–529.
Vinogradov, S., Fisher, M., de Villers-Sidani, E., 2012. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology 37, 43–76.
Volkow, N.D, Wang, G.J., Tomasi, D., Kollins, S.H., Wigal, T.L., Newcorn, J.H., Telang, F.W., Fowler, J.S., Logan, J., Wong, C.T., Swanson, J.M., 2012. Methylphenidate-elicited dopamine increases in ventral striatum are associated with long-term symptom improvement in adults with attention deficit hyperactivity disorder. J Neurosci. 32, 841–849.
Von Hohenberg, C.C., Pasternak, O., Kubicki, M., Ballinger, T., Vu, M.A., Swisher, T., Green, K., Giwerc, M., Dahlben, B., Goldstein, J.M., Woo, T.U., Petryshen, T.L., Mesholam-Gately, R.I., Woodberry, K.A., Thermenos, H.W., Mulert, C., McCarley, R.W., Seidman, L.J., Shenton, M.E., 2014. White matter microstructure in individuals at clinical high risk of psychosis: a whole-brain diffusion tensor imaging study. Schizophr. Bull. 40, 895–903.

Wager, T.T., Hou, X., Verhoest, P.R., Villalobos, A., 2010. Moving beyond rules: the development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of drug-like properties. ACS Chem. Neurosci. 1, 435–449.

Wallace, D.C., 2013. A mitochondrial bioenergetics etiology of disease. J Clin Invest. 123, 1405–1412.

Wang, H., Duclot, F., Liu, Y., Wang, Z., Kabbaj, M., 2013. Histone deacetylase inhibitors facilitate partner preference formation in female prairie voles. Nat. Neurosci. 16, 919–924.

Wang, K., Li, M., Hakonarson, H., 2010. Analysing biological pathways in genome-wide association studies. Nat. Rev. Genet. 11, 843–854.

Wang, X., Sliwoski, G.R., Buttner, E.A., 2011. The relevance of *Caenorhabditis elegans* genetics for understanding human psychiatric disease. Harv. Rev. Psychiatry 19, 210–218.

Wang, X.J., Krystal, J.H., 2014. Computational psychiatry. Neuron 84, 638–654.

Warmerdam, L., van Straten, A., Jongsma, J., Twisk, J., Cuijpers, P., 2010. Online cognitive behavioral therapy and problem-solving therapy for depressive symptoms: exploring mechanisms of change. J. Behav. Ther. Exp. Psychiatr. 41, 64–70.

Watanabe, N., Omori, I.M., Nakagawa, A., Cipriani, A., Barbui, C., Churchill, R., Furukawa, T.A., 2011. Mirtazapine versus other antidepressive agents for depression. Cochrane Database Syst. Rev., 7 (CD006528).

Watkins, C.C., Sawa, A., Pomper, M.G., 2014. Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. Transl. Psychiatry 4, e350.

Watson, D.J., Loiseau, F., Ingallinesi, M., Millan, M.J., Marsden, C. A., Fone, K.C., 2012. Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: a key role for the prefrontal cortex. Neuropsychopharmacology 37, 770–786.

Webb, C.A., Derubeis, R.J., Hollon, S.D., Dimidjian, S., Amsterdam, J.D., Shelton, R.C., 2013. Convergence and divergence in the delivery of cognitive therapy in two randomized clinical trials. Behav. Res. Ther. 51, 493–498.

Weinberg, R.A., 2010. Point: hypotheses first. Nature, 464; , 678.

Weksler, M.E., Szabo, P., Relkin, N.R., Reidenberg, M.M., Weksler, B.B., Coppus, A.M., 2013. Alzheimer's disease and Down's syndrome: treating two paths to dementia. Autoimmun. Rev. 12, 670–673.

Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., Garland, A., Hollinghurst, S., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., Turner, K., Williams, C., Peters, T., Lewis, G., 2013. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomized controlled trial. Lancet 381, 375–384.

Williams, G., Denny-Gouldson, P., 2013. Informatics the same old problems, just bigger. Drug Discov. World 14 (Winter), 28.

Wilson, C.A., Koenig, J.I., 2014. Social interaction and social withdrawal in rodents as readouts for investigating the negative symptoms of schizophrenia. Eur. Neuropsychopharmacol. 24, 759–773.

Winchester, C.L., Pratt, J.A., Morris, B.J., 2014. Risk genes for schizophrenia: translational opportunities for drug discovery. Pharmacol. Ther. 143, 34–50.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., Van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679.

Wong, D.T., Fuller, R.W., Robertson, D.W., 1990. Fluoxetine and its two enantiomers as selective serotonin uptake inhibitors. Acta Pharm. Nord. 2, 171–180.

Wong, D.T., Perry, K.W., Bymaster, F.P., 2005. Case history: the discovery of fluoxetine hydrochloride (Prozac). Nat. Rev. Drug Discov. 4, 764–774.

Wong, E.H., Tarazi, F.I., Shahid, M., 2010. The effectiveness of multi-target agents in schizophrenia and mood disorders: relevance of receptor signature to clinical action. Pharmacol. Ther. 126, 173–185.

Woodcock, J., 2010. Precompetitive research: a new prescription for drug development? Clin. Pharmacol. Ther. 87, 521–523.

Wyss-Coray, T., Rogers, J., 2012. Inflammation in Alzheimer disease – a brief review of the basic science and clinical literature. Cold Spring Harb. Perspect. Med. 2, a006346.

Youdim, M.B., Wadia, A., Tatton, W., Weinstock, M., 2001. The anti-Parkinson drug rasagiline and its cholinesterase inhibitor derivatives exert neuroprotection unrelated to MAO inhibition in cell culture and in vivo. Ann. NY Acad. Sci. 939, 450–458.

Zarate, C.A., Mathews, D., Ibrahim, L., Chaves, J.F., Marquardt, C., Ukoh, I., Jolkovsky, L., Brutsche, N.E., Smith, M.A., Luckenbaugh, D.A., 2013. A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. Biol. Psychiatry 74, 257–264.

Zarate, C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry 63, 856–864.

Zeller, E.A., Barsky, J., Berman, E.R., Fouts, J.R., 1952. Action of isonicotinic acid hydrazide and related compounds on enzymes involved in the autonomic nervous system. J. Pharmacol. 106, 427–428.

Zhang, T., Koutsouleris, N., Meisenzahl, E., Davatzikos, C., 2015. Heterogeneity of structural brain changes in subtypes of schizophrenia revealed using magnetic resonance imaging pattern analysis. Schizophr. Bull. 41, 71–84.

Zhang, T.Y., Meaney, M.J., 2010. Epigenetics and the environmental regulation of the genome and its function. Annu. Rev. Psychol. 61, 439–466.

Zhao, H., Guo, Z., 2009. Medicinal chemistry strategies in follow-on drug discovery. Drug Discov. Today 14, 516.

Zhu, Y., Watson, J., Chen, M., Shen, D.R., Yarde, M., Agler, M., Burford, N., Alt, A., Jayachandra, S., Cvijic, M.E., Zhang, L., Dyckman, A., Xie, J., O'Connell, J., Banks, M., Weston, A., 2014. Integrating high-content analysis into a multiplexed screening approach to identify and characterize GPCR agonists. J. Biomol. Screen. 19, 1079–1089.

Zipursky, R.B., Reilly, T.J., Murray, R.M., 2013. The myth of schizophrenia as a progressive brain disease. Schizophr. Bull. 39, 1363–1372.

Zohar, J., Nutt, D.J., Kupfer, D.J., Moller, H.J., Yamawaki, S., Spedding, M., Stahl, S.M., 2014. A proposal for an updated neuropsychopharmacological nomenclature. Eur. Neuropsychopharmacol. 24, 1005–1014.