Drug treatment developments in schizophrenia and bipolar mania: latest evidence and clinical usefulness

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Abstract: Schizophrenia and bipolar disorder are often highly debilitating with chronic courses, and psychotropic drugs represent cornerstones in the treatment. The primary aim of the review was to summarize the latest evidence with regards to the efficacy and effectiveness of drug treatment of schizophrenia and the manic phases of bipolar disorder. Schizophrenia systematic reviews conclude that antipsychotic drugs are effective in treating overall symptoms of psychosis and in preventing relapse. Some of the newer agents, the second-generation antipsychotics (SGAs), have demonstrated superiority compared with the older first-generation drugs and other SGAs but side-effect differences among the drugs are of a greater magnitude than effect differences. The pragmatic randomized trials of effectiveness have shown a longer time until treatment discontinuation for olanzapine compared with other antipsychotics. Cohort studies have found superiority for the long-acting injection formulations compared with the oral formulations of the drugs, and lower total mortality risk in users of antipsychotics compared with non-users. In bipolar mania SGAs have shown superior antimanic efficacy compared with other mood-stabilizing drugs. In conclusion antipsychotics, in particular some of the SGAs, seem to be drugs of first choice for both schizophrenia and bipolar mania. This perspective review focused on mean effects but the group means may not always be particularly useful as schizophrenia and bipolar mania are biologically heterogeneous disorders with large inter-individual variations in drug response and tolerance. In patients with a prior drug history the different pharmacological and clinical profiles may be exploited in subsequent choices of drugs.

Keywords: mania, psychotropic drugs, review, schizophrenia

Introduction

Schizophrenia has a lifetime prevalence of about 1% in the general population whereas the corresponding joint estimate for bipolar I and II disorder is at least 1% and increases to 3% or more if subthreshold bipolar disorder is included [Kessler *et al.* 2012; Merikangas *et al.* 2011; Perala *et al.* 2007], and are among the most severe mental illnesses, with excessive physical comorbidity and greatly reduced life expectancy compared with the general population [De Hert *et al.* 2011]. The active phases of the disorders are associated with highly debilitating symptoms, and severe manias and schizophrenic psychosis cause the most serious behavioural disturbances. Active psychosis has been ranked among the most disabling disorders by severity in the general population, and more disabling than paraplegia, blindness, or HIV infection [Ustun *et al.* 1999]. The majority of patients experience a chronic relapsing-remitting course of the disorders [Altamura *et al.* 2011; Bromet and Fennig, 1999]. Although not the focus of the present review it should be emphasized that the depressive phase of bipolar disorders is far more common and associated with more impairment than the manic phase; see for example Kupka and collaborators, Rosa and collaborators, and Merikangas and collaborators for an update [Kupka *et al.* 2007; Merikangas *et al.* 2011; Rosa *et al.* 2010]. For some time the sharp dichotomy between schizophrenia and bipolar disorder has been challenged based on findings of

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Table 1. Affinities of selected antipsychotic drugs for some central receptors in the brain. (Adapted from Abi-Dargham and Laruelle [2005], Miyamoto *et al*. [2005], and Roth *et al*. [2004].)

Antipsychotics		Receptors								
Class	Drug	D1	D2	D3	D4	5HT1A	5HT2A	5HT2C	H1	M1
FGA	Chlorpromazine	+	+++	+++	++	–	+++	++	++++	++
	Haloperidol	++	++++	+++	+++	–	++	–	++	–
SGA	Clozapine	++	+	+	++	+	++	++	+++	+++
	Risperidone	+	+++	+++	+++	+	++++	++	++	-
	Olanzapine	++	++	++	++	–	+++	++	+++	+++
	Quetiapine	+	+	+	++	+	++	–	++	+
	Ziprasidone	+	+++	+++	++	+++	++++	++	++	–
	Amisulpride	–	+++	+++	–	–	–	–	–	–
TGA	Aripiprazole	+	++++*	++++	++	+++	+++	+	–	–

*Partial agonist to the DA dopamine 2 receptor.
5-HT1A-2C, 5-hydroxytryptamine (serotonine) receptor types 1A–2C; D1–D4, dopamine receptors 1–4; FGA, first-generation antipsychotic; H1, histamine receptor 1; M1, muscarine receptor 1. SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

a partly shared genetic susceptibility pattern, in addition to psychotic symptoms being prevalent in mania, and affective symptoms being common in patients with schizophrenia [Qian *et al.* 2012]. Moreover, some of the pharmaceutical interventions are the same. Psychotropic drugs have represented cornerstones in the treatment of both disorders ever since the discoveries of the antimanic and antipsychotic effects of lithium and chlorpromazine respectively [Delay *et al.* 1952; Lenox and Watson, 1994].

Numerous new agents have been synthesized in the years following chlorpromazine [Shen, 1999] (Table 1). Unveiled a decade after the launch of chlorpromazine, all antipsychotics antagonize dopaminergic transmission at the dopamine D2 receptor subtype, which has proven to be essential to the antihallucinatory and antidelusional effects of the drugs [Howes and Kapur, 2009]. The potent D2-blocking property of the early antipsychotics is also associated with hyperprolactinaemia and the extrapyramidal syndrome (EPS), including Parkinsonism, akathisia and tardive dyskinesias, which was considered by many an obligatory side effect until the demonstration of clozapine's 'atypical' combination of stronger antipsychotic action without causing significant EPS or prolactin elevation [Cookson *et al.* 2012; Hippius, 1989]. The class of drugs following clozapine aimed at mimicking the 'atypical' properties, and was accordingly termed *atypicals* or second-generation antipsychotics (SGAs) as opposed to the older typical or first-generation drugs (FGAs). Pharmacologically, the SGAs are characterized by the combination of potent antagonism at the serotonergic 5-hydroxytryptamine (serotonine) receptor type 2A (5HT2A) receptor and weaker D2 antagonism, whereas the FGA group more potently and selectively block the D2 receptor [Meltzer and Massey, 2011]. Amisulpride does selectively antagonize dopaminergic receptors but is often categorized among the SGAs due to its atypical clinical profile [McKeage and Plosker, 2004]. Indeed, both FGAs and SGAs are heterogeneous drug classes targeting a number of additional receptor systems. Aripiprazole, one of the latest antipsychotics and sometimes referred to as a third-generation antipsychotic agent, has a unique pharmacological profile as it is a partial agonist to the D2 receptor [Swainston Harrison and Perry, 2004]. However, clozapine remains the superior antipsychotic drug in schizophrenia, in particular in patients with treatment-resistant psychotic symptoms [Asenjo Lobos *et al.* 2010; Kane and Correll, 2010; Wahlbeck *et al.* 2000].

In bipolar disorders the group of mood-stabilizing agents (mood stabilizers), although lacking a clear-cut definition of the term, are the treatments of choice [Altamura *et al.* 2011]. Several new drugs and classes of mood-stabilizing drugs have been introduced since lithium, including anticonvulsants and SGAs [Altamura *et al.* 2011] (Table 2). The mood-stabilizing mechanisms of action of these drugs remain only partially known, with effects on ion channels and neurotransmitters among others; see Altamura and colleagues for a

Table 2. Selected mood-stabilizing drugs. (Based on Altamura *et al*. [2011].)

Drug	Selected putative mechanisms of mood-stabilizing action
Lithium	Inhibition of inositol monophosphatase → ↓ protein kinase C activity
	Inhibition of GSK-3 → ↓ protein kinase C activity/altered cellular differentiation
	Stabilization of DA and cholinergic receptors
	Normalization of low CSF GABA
	Normalization of intracellular sodium
	Increase of Glu uptake
	Reduced myoinositol synthesis
Anticonvulsants	Inhibition of sodium channels
Valproate	Inactivation of GSK-3
	Interaction with DA, GABA and Glu transmission
	Reduced myoinositol synthesis
Carbamazepine	Reduced Glu and catecholamine release
	Reduced myoinositol synthesis
Lamotrigine	
Second-generation antipsychotics	DA receptor antagonism
	5-HT2 receptor antagonism
Olanzapine	GSK-3 regulation (olanzapine)
Quetiapine	Blocking of norepinephrine transporter (quetiapine)
Risperidone	
Aripiprazole	
Asenapine	
Clozapine	

5-HT2, 5-hydroxytryptamine (serotonin) receptor type 2; CSF, cerebrospinal fluid; DA, dopamine; GABA, γ amino butyric acid; Glu, glutamate; GSK-3, glycogen synthetase kinase 3.

review [Altamura *et al.* 2011]. Lithium has also been used for the treatment of symptoms in patients with schizophrenia but evidence for beneficial effects in schizophrenia has not been established [Leucht *et al.* 2007]. Also anticonvulsants, for example valproate, have been used for treating schizophrenia but without firm evidence from randomized controlled trials (RCTs) as identified by a 2008 Cochrane review and further studies on the antiaggressive effects of valproate for patients with schizophrenia are recommended [Schwarz *et al.* 2008].

For several reasons there has been paucity in the development of molecules with novel mechanisms of action for bipolar mania and schizophrenia reaching clinical practice [Miller, 2010; Williams, 2011]. In schizophrenia a number of new drugs which target receptors outside the dopaminergic system are being explored, the most promising ones addressing glutamatergic and cholinergic receptor systems, but none are available thus far for regular use and antipsychotic drugs that antagonize dopaminergic transmission remain the only drug class that targets the psychotic symptoms in schizophrenia [Biedermann and Fleischhacker, 2011; Miyamoto *et al.* 2012]. Even so, great research efforts have been made in recent years to deliver new evidence regarding the drug treatment. In schizophrenia some of the leading issues and controversies in antipsychotic drug treatment include which drug class or single drug should be regarded as first choice, as reflected in the differences among treatment guidelines [Gaebel *et al.* 2005, 2011]. Other issues being debated are those of the place of different drug formulations of antipsychotics [oral *versus* long-acting injections (LAIs)] in the treatment algorithms as partial or nonadherence to oral drugs remains a major issue in antipsychotic drug treatment, with up to 75% of patients being only partially adherent to their drug regimens after the first year of treatment and nonadherence being one of the leading causes of psychotic

relapse [Leucht and Heres, 2006]; and finally whether antipsychotic drug use increases overall mortality risk. In the treatment of mania, SGAs are the most lately introduced mood stabilizers, and main issues of debate are which mood stabilizers should be agents of first choice, as reflected in differences among the latest treatment guidelines [Altamura *et al.* 2011].

Systematic reviews of RCTs are generally regarded at the top of the evidence hierarchy (see http://www.cebm.net/index.aspx?o=1025). In the last decade, however, concerns about methodological limitations have been pointed to in schizophrenia and mania drug trials, including the highly selected patient samples representing as low as 10% of the population under investigation, the short trial durations, and the rigid experimental designs of classical RCTs of efficacy, making inference to the population in question problematic [Leucht *et al.* 2008; Licht, 2002; March *et al.* 2005; Stroup *et al.* 2006]. The pragmatic or practical RCT design has been launched to address some of the limitations [Depp and Lebowitz, 2007; March *et al.* 2005]. Pragmatic trials, also known as effectiveness trials, address how a treatment works under normal clinical circumstances with longer follow up and more heterogeneous samples, thus reflecting the patients seen in regular clinical practice. Another distinguishing feature of the pragmatic trials is the inclusion of global outcome measures, considered to be more clinically relevant than mere rating scales, such as time until drug discontinuation; time until discharge from hospital, and time until rehospitalization. The issue of how representative the samples really are still remains a major concern in the effectiveness studies and represents one of the most important selection problems [Leucht *et al.* 2008], making the case for observational studies to complement the evidence base [Haddad *et al.* 2011; McCombs *et al.* 2011]. Finally, the potential bias imposed by study sponsorship has been highlighted [Heres *et al.* 2006; Perlis *et al.* 2005], and pragmatic trials funded independently of the pharmaceutical industry have been called for [Nasrallah, 2007].

The aim of the present perspective review is to assess the latest evidence on the efficacy and effectiveness of drugs in treating symptoms of schizophrenia and mania respectively. Results are drawn from recent systematic reviews of RCTs, pragmatic trials, and cohort studies, as these might be considered complimentary.

Methods

PubMed was searched for systematic reviews, pragmatic studies and cohort studies published in the last 10 years in adult populations with schizophrenia or bipolar mania. The most recent and comprehensive systematic reviews were chosen for the present perspective review. As a result of the steadily increasing number of meta-analyses, the systematic reviews of meta-analyses have emerged in some areas [Delgado-Rodriguez, 2006]. These were particularly searched for. Only pragmatic studies with randomization procedures were regarded as of sufficient methodological quality for the review. Major large and well reported cohort studies were also considered relevant for the review.

The primary outcomes were symptom reduction (mania and symptoms of psychosis respectively), and tolerability. Other areas of efficacy outcomes were also frequently reported, including antidepressive and neurocognitive effects, but were regarded outside the scope of the present review. EPS and metabolic disturbances, including weight gain and adverse influences on glucose and serum lipids, were chosen as tolerability outcomes for the review, as these have received particular attention. In addition, the special situation of use of mood stabilizers in pregnancy is reviewed because of the potential teratogenicity of the drugs. The review focuses on monotherapy as this is the preferred first-line treatment strategy according to recent evidence and most treatment guidelines for schizophrenia and mania respectively [Kroken and Johnsen, 2012; Nivoli *et al.* 2012].

Results

Schizophrenia

Systematic reviews of randomized controlled trials. Several systematic reviews of antipsychotic drug efficacy have been published in the last few years. Leucht and colleagues recently published three meta-analyses on the efficacy and tolerability of oral antipsychotics for schizophrenia [Leucht *et al.* 2009a, 2009b, 2009c]. In the comparisons of SGAs *versus* placebo based on 38 RCTs and 7323 participants, all the antipsychotics were superior to placebo, with moderate effect sizes (ES) of about 0.5 in reducing overall psychotic symptoms [Leucht *et al.* 2009a]. The numbers needed to treat (NNT) were five and six for relapse prevention and responder status respectively. Almost all the included studies were of short duration. In the

SGA *versus* FGA meta-analysis based on 150 double-blind RCTs with 21,533 participants, the SGAs amisulpride, clozapine, olanzapine, and risperidone were significantly superior to the FGAs in reducing overall symptoms of psychosis, with effect sizes between 0.1 and 0.5, whereas the other SGAs under investigation (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) performed equally to the FGAs [Leucht *et al.* 2009b, 2009c]. The same pattern was also found for positive and negative symptoms of psychosis respectively. The SGAs had less EPS than haloperidol. The SGAs except aripiprazole and ziprasidone were associated with more weight gain than haloperidol. In the meta-analysis on head-to-head comparisons of SGAs, including 78 studies with 13,558 participants, olanzapine was superior to aripiprazole, quetiapine, risperidone, and ziprasidone, and not different from amisulpride and clozapine for overall symptoms of psychosis [Leucht *et al.* 2009c]. Risperidone was superior to quetiapine and ziprasidone. In line with this, Klemp and collaborators, using a Bayesian meta-analytic approach, found the following response ratios for SGAs and haloperidol compared with placebo: clozapine > olanzapine > risperidone > aripiprazole > haloperidol [Klemp *et al.* 2011]. In a very recent systematic review of meta-analyses, Citrome included 91 reports on oral antipsychotics for schizophrenia [Citrome, 2012]. Importantly, amisulpride and sertindole were left out of the review as these drugs are not approved in the USA. The author concluded that clozapine followed by olanzapine and risperidone were found to be the most efficacious oral antipsychotic drugs.

Antipsychotic maintenance treatment demonstrated marked relapse prevention compared with placebo in a meta-analysis based on 116 reports with 6493 patients [Leucht *et al.* 2012b]. In the group using antipsychotics, 27% relapsed between 7 and 12 months of follow up, whereas 64% relapsed in the placebo group, the relative risk (RR) being 0.35 and the NNT was three. Ten percent of patients using antipsychotics were readmitted in the same period of time compared with 25% in the placebo groups (RR 0.39), the NNT being seven. Importantly, the relapse reduction effect was also unaltered in patients who had been in remission for several years. No differences were found between the SGA and FGA classes in relapse prevention. Kishimoto and colleagues found a small superiority of SGAs compared with FGAs for relapse prevention in their systematic review of head-to-head comparisons [Kishimoto *et al.* 2011]. Álvarez-Jiménez and colleagues found only a trend for superiority of FGAs compared with placebo in relapse prevention after a first episode of psychosis [Álvarez-Jiménez *et al.* 2011]. For comparisons between different routes of antipsychotic drug administration, 10 studies lasting 1 year or longer with 1700 participants and comparing depot to oral formulation were included in a meta-analysis [Leucht *et al.* 2011a]. The included depot antipsychotics were fluphenazine depot, risperidone LAI, haloperidol decanoate, and zuclopenthixol depot. Relapses occurred in 22% *versus* 33% in the depot and oral groups respectively. There were no differences between the groups with respect to rehospitalization rates due to psychopathology. The authors stated the finding of superiority for the depot formulation with regards to relapse prevention; however, they point to potential bias. Indeed Leucht and colleagues mention in their meta-analysis on maintenance therapy that an unpublished update on the depot *versus* oral meta-analysis shows no difference among the formulations [Leucht *et al.* 2012b].

As a class, SGAs have demonstrated lower propensities for EPS compared with high-potency FGAs such as haloperidol, but only a few SGAs had lower EPS-inducing propensities compared with low-potency FGAs [Leucht *et al.* 2009b]. Moreover, the SGAs were not associated with more EPS than placebo in the SGA *versus* placebo meta-analysis [Leucht *et al.* 2009a]. In a 2012 meta-analysis with head-to-head comparisons of SGAs based on 54 studies with predominantly chronic patients, differences among the SGAs were found [Rummel-Kluge *et al.* 2012]. Risperidone produced more EPS than most other SGAs except amisulpride and aripiprazole. A dose–response relationship was found. Quetiapine seemed to have the lowest propensity for EPS in this chronic-phase meta-analysis. Haddad and collaborators performed a systematic review in first episode psychosis based on 11 trials including open effectiveness studies [Haddad *et al.* 2012]. Haloperidol was associated with more EPS than the SGAs, even in low doses of haloperidol. In one of the included studies, first-episode patients had more EPS than multiepisode patients. Crossley and colleagues performed a meta-analysis in early psychosis and found a significant advantage for SGAs over FGAs regarding Parkinsonism [Crossley *et al.* 2010]. One particular form of EPS, the tardive or late dyskinesias (TD), has been investigated in a 2004 systematic review of studies with at least

1-year of follow up [Correll *et al.* 2004], and with a 2008 update [Correll and Schenk, 2008]. In the first review the annual incidence of TD was 0.8% and 5.4% for SGAs and haloperidol respectively in adult populations [Correll *et al.* 2004]. There were differences among the SGAs with regards to TD incidence, and higher annual incidence in the older population. In the 2008 update the annual TD incidence in adults was 3.0% and 7.7% for the SGA- and FGA-treated patients respectively [Correll and Schenk, 2008].

SGAs have demonstrated higher weight gain propensities compared with FGAs in early psychosis, amounting to 2.1 kg on average [Crossley *et al.* 2010]. Five of the seven included studies on which the estimate was based lasted 1–2 years. Rummel-Kluge and colleagues conducted a meta-analysis based on 48 RCTs of head-to-head comparisons among the SGAs [Rummel-Kluge *et al.* 2010]. Clozapine and olanzapine were associated with the greatest weight gain, glucose and cholesterol elevation, followed by quetiapine, risperidone, and sertindol, followed by amisulpride and aripiprazole, with ziprasidone showing the least elevations. In absolute figures the biggest difference among the SGAs during the 2–6-month study durations amounted to 4 kg. Importantly, the authors identified an effect of sponsorship as the sponsor's drugs were associated with more beneficial metabolic developments [Rummel-Kluge *et al.* 2010]. Smith and collaborators conducted a meta-analysis of head-to-head comparisons of SGAs *versus* FGAs on the risk of diabetes mellitus [Smith *et al.* 2008].The relative risk of diabetes was 1.32 for those prescribed a SGA compared to those prescribed a FGA. The authors stated that there were several methodological limitations to the studies included in the meta-analysis, however.

Pragmatic studies of effectiveness. Major pragmatic studies of antipsychotic effectiveness include the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [Lieberman *et al.* 2005], and the UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) [Jones *et al.* 2006], both including patients with chronic schizophrenia; and the European First-episode Schizophrenia Trial (EUFEST) [Kahn *et al.* 2008], and the US Comparison of Atypicals in First Episode of Psychosis (CAFÉ) study [McEvoy *et al.* 2007], both recruiting acute-phase patients. Smaller pragmatic studies include the Norwegian Bergen Psychosis Project [Johnsen *et al.* 2010] and the Japanese Acute Phase Study by Hatta and collaborators [Hatta *et al.* 2009].

In a systematic review based on 16 randomized pragmatic head-to-head studies of SGAs published before 2008, the most consistent finding was a longer time to treatment discontinuation for those treated with olanzapine in chronic phase schizophrenia but not in the first-episode or acute-phase studies [Johnsen and Jorgensen, 2008]. In the review no consistent differences among the drugs were disclosed for symptom reduction across the studies. The olanzapine groups had more metabolic side effects compared with the other groups but otherwise there were few distinct side-effect differences among the SGAs. The FGA-treated patients experienced more EPS compared with those treated with FGAs. The primary outcomes of the EUFEST study were published after the systematic review and were thus not included. In comparing the SGAs amisulpride, olanzapine, quetiapine, and ziprasidone, and haloperidol in 498 first-episode patients, the SGAs had longer times to discontinuation compared with haloperidol, and amisulpride and olanzapine had the largest advantages in this regard [Kahn *et al.* 2008]. There were no differences among the comparators with regards to reduction of psychotic symptoms but amisulpride had the most beneficial change of overall severity of illness and functioning. There were differences among the antipsychotics with regards to which drugs were associated with the highest frequency of the various side effects: akathisia (haloperidol and ziprasidone) and Parkinsonism (haloperidol); weight change from baseline (olanzapine); hyperprolactinemia (amisulpride) [Kahn *et al.* 2008]. CUtLASS included 227 patients with schizophrenia eligible for change of medication because of inadequate effect or side effects, and followed the patients for 12 months [Jones *et al.* 2006]. The patients were randomized to receive a SGA or a FGA, with the choice of particular agent left at the treating clinician's discretion. The primary outcome was the quality-of-life score and no differences among the SGA and FGA groups were found. There were no differences among the groups with regards to the secondary outcomes related to effects and adverse effects. The Bergen Psychosis Project randomized 213 patients admitted with acute psychosis to olanzapine, quetiapine, risperidone, or ziprasidone, and followed the patients for up to 2 years [Johnsen *et al.* 2010]. The quetiapine group had

the most beneficial outcome with regards to overall reduction of psychosis and global severity of illness, as well as increasing functioning. The tolerability outcomes were comparable among the groups, except for more increase of the hip circumference in the olanzapine group and more galactorrhoea in the risperidone group. Hatta and colleagues compared olanzapine, quetiapine, risperidone, and ziprasidone in 80 patients with acute-phase schizophrenia in an 8-week study and found olanzapine and risperidone to be the superior drugs with regards to time to treatment discontinuation [Hatta *et al.* 2009]. No tolerability differences among the drug groups were disclosed. Lastly, Glick and colleagues performed a meta-analysis of studies lasting 3 months and more, including pragmatic and naturalistic studies [Glick *et al.* 2011]. The meta-analysis largely confirmed the findings from short-term studies, with clozapine, olanzapine, and risperidone being the most efficacious antipsychotics but clozapine and olanzapine also having the greatest weight gain and adverse metabolic influences.

Cohort studies. Tiihonen and collaborators recently published nationwide cohort studies from Finland [Tiihonen *et al.* 2009, 2011]. In a cohort of 66,881 patients with schizophrenia and 11 years of follow up, the clozapine-treated patients had the lowest overall mortality risk [Tiihonen *et al.* 2009]. Moreover, antipsychotic drug use was associated with lower mortality risk than no use. In patients with schizophrenia followed after discharge from their first hospital admission the risk of rehospitalization was only about one-third in those treated with the depot formulations compared with the oral formulations of the drugs [Tiihonen *et al.* 2011]. The mortality risk associated with the use of antipsychotic drugs was about half the risk associated with no use. The use of any antipsychotic drug was associated with less than half the risk of rehospitalization compared with no use. This finding corresponds to that of Kroken and colleagues in a consecutive cohort of all patients with schizophrenia discharged from a catchment area mental hospital, in which the risk of rehospitalization was reduced by 75% in patients receiving one antipsychotic drug compared with no use [Kroken *et al.* 2011].

Synthesis and discussion. Based on the most recent evidence, antipsychotic drugs are effective in the treatment of schizophrenia, with moderate effect sizes compared with placebo and NNTs of about five. The effect sizes are comparable to those of the majority of general medicine drugs [Leucht *et al.* 2012a]. Moreover, compared with placebo, antipsychotics markedly reduce the risks of relapse of psychosis and of rehospitalization, with up to a 75% reduction of risk as demonstrated in both RCTs of efficacy and cohort studies with long follow ups. The use of antipsychotics is associated with a reduced overall mortality risk compared with no use.

Meta-analyses primarily based on RCTs of efficacy indicate differential efficacy among the agents. The SGAs amisulpride, clozapine, olanzapine, and risperidone have demonstrated significant superiority compared with FGA comparators, mostly haloperidol, and other SGAs on the reduction of psychosis. The effect sizes are small, however, and much smaller than the adverse effect differences among the drugs. The FGAs are associated with more EPS, whereas the SGAs produce more weight gain and metabolic adverse effects. However, in line with the efficacy differences, there are variations in both the FGA and SGA groups with regards to adverse effects propensities, thus making the distinction between FGAs and SGAs less meaningful. The efficacy differences have not been robustly replicated in the pragmatic, randomized studies, which may indicate that differences of smaller magnitude are levelled out in the more heterogeneous samples of effectiveness trials, allowing for the concomitant use of other psychotropics. One exception is the finding of superiority for quetiapine in the Bergen Psychosis Project (a 24-month, prospective, rater-blind, naturalistic, randomized, head-to-head comparison of the effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone) on several outcomes which challenges the results of the efficacy trials and other pragmatic studies [Johnsen *et al.* 2010]. The same phenomenon of less clear-cut differences among the drugs seems to be the case for the adverse effects, although olanzapine and clozapine are consistently found to cause the most weight gain and other metabolic adverse effects. Importantly, however, although almost 90% of the first-episode patients treated with olanzapine in the EUFEST study [Kahn *et al.* 2008] gained more than 7% of their baseline weight, this was also the case for almost 40% of the patients treated with ziprasidone, an antipsychotic agent generally regarded as being among the most 'weight neutral' antipsychotics [Newcomer, 2007]. This may point to a higher propensity for weight gain in the early phase patients. The 2009 update of the Schizophrenia

patient outcomes research team (PORT) treatment recommendations [Buchanan *et al.* 2010] actually does not consider olanzapine a first-line treatment in first-episode schizophrenia because of the metabolic concerns associated with the drug.

One of the most consistent findings in the pragmatic studies is the longer time until treatment discontinuation for olanzapine, despite the highest rates of weight gain and other metabolic adverse effects in olanzapine-treated patients. Thus far, the heightened metabolic load of the SGAs has not led to increased cardiovascular mortality rates in patients with schizophrenia, as demonstrated in the Finnish cohort study [Tiihonen *et al.* 2009]. In a meta-analysis of RCTs the depot formulation did not convincingly demonstrate superiority to the oral formulations in relapse prevention, whereas a strong protective effect of the depots was found in the Finnish cohort. The evaluation of the value of depot antipsychotics may represent an area where the RCT design has profound shortcomings related to selection issues [Haddad *et al.* 2011].

Principal limitations to the systematic reviews are that they are predominantly based on RCTs of short duration and with highly selected samples [Citrome, 2012]. Moreover, attrition rates are substantial during follow up. The pragmatic studies have supplemented the evidence base, particularly with respect to the global outcomes, but do come with limitations; see Naber and Lambert for a review of important methodological problems in the CATIE and CUtLASS studies [Naber and Lambert, 2009].

Bipolar mania

Systematic reviews of randomized controlled trials. Cipriani and collaborators have undertaken a recent meta-analysis of antimanic drugs in acute mania based on 68 trials including 16,073 patients, with the mean duration of trials being 3.4 weeks [Cipriani *et al.* 2011]. The included drugs were aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. Compared with placebo, the drugs were significantly superior for the primary outcome, change of the Young Mania Rating Scale, with the exception of topiramate and lamotrigine. The effect sizes were moderate. As a group the antipsychotics were more effective than the (other) mood stabilizers. Haloperidol, olanzapine, and risperidone had the highest efficacy compared with the other drugs. Olanzapine and risperidone also ranked highest on acceptability. The efficacy results compared with placebo correspond to those of earlier reviews, which also included trials with duration up to 12 weeks [Derry and Moore, 2007; Smith *et al.* 2007]. However, antipsychotics did cause more weight gain and extrapyramidal side effects compared with placebo. Tarr and colleagues performed another recent meta-analysis of head-to-head monotherapy RCTs of SGAs *versus* mood stabilizers in acute mania, including nine studies with the SGAs olanzapine, quetiapine, risperidone, and aripiprazole, and the mood stabilizers lithium and valproate [Tarr *et al.* 2011]. The included studies lasted for 3–4 weeks. The meta-analysis found a superiority for the SGAs with regards to change of the mania rating scales (standardized mean difference –0.22), as well as responder rates (7% higher for the SGAs; number needed to treat 17), and dropout rates (5% lower for the SGAs). In their systematic review on relapse prevention Beynon and colleagues found olanzapine, aripiprazole, and lithium to be superior to placebo in preventing manic relapse [Beynon *et al.* 2009].

Pragmatic studies of effectiveness. Licht and colleagues randomized 155 patients with bipolar 1 disorder to lamotrigine or lithium maintenance treatment after an index episode of mania, mixed episode, or depression [Licht *et al.* 2010]. The included patients had more than one episode before the index episode. The primary end points were the need for additional psychotropics or hospitalization. Although lithium performed numerically better than lamotrigine with regards to the mania-related end points, the difference was not statistically significant.

Cohort studies. Kessing and colleagues conducted two nationwide population-based register linkage studies with up to 12 years of follow up for 11,404 patients with a diagnosis of bipolar disorder [Kessing *et al.* 2011, 2012]. They found an increased risk of psychiatric rehospitalization for patients with a manic index episode who were treated with lamotrigine compared with lithium [Kessing *et al.* 2011]. In the comparisons between valproate and lithium, valproate-treated patients had an increased hazard rate for hospital admissions due to a manic or mixed episode [Kessing *et al.* 2012].

Regarding the use of mood stabilizers in pregnancy, Galbally and collaborators conducted a systematic review based on cohort studies and case series of lithium and antiepileptic drugs [Galbally *et al.* 2010]. Lithium has historically been associated with an increased risk of the Ebstein's anomaly, a cardiovascular malformation occurring at a rate of 0.005% in the general population. The initially high lithium-associated risk estimates have been downregulated as more data have become available and the current risk estimate is between 0.05% and 0.01%. Sodium valproate is consistently found to be associated with neural tube defects, cranio-facial defects, as well as limb and cardiac malformations, and with poorer neurodevelopmental outcomes, among others. The malformation rates associated with sodium valproate varied from 4% to 20% among the studies included in the systematic review. Carbamazepine shares the association with a variety of malformations, though at lower rates (3% overall) compared with sodium valproate. Moreover carbamazepine is associated with reduced head circumference and reduction of birth weight and length. The results for lamotrigine, though not a first-line antimania agent, are less uniform with regards to potential teratogenicity.

Gentile did a very comprehensive systematic review on antipsychotics in pregnancy, including both animal and human studies [Gentile, 2010]. The data are sparse, especially for the SGAs, and restricted to case reports for the most part, whereas there is a richer literature for some of the FGAs. There are some indications of increased teratogenicity within both the SGA and FGA groups, but the different reports do not seem to be consistent with regards to types of ma1formations associated with the use of antipsychotics. Based on the available data chlorpromazine seems to be among the safest alternatives.

Synthesis and discussion. In general, the evidence base regarding the treatment of mania is much smaller than that for schizophrenia. Recent systematic reviews demonstrate that most mood stabilizers are superior to placebo in decreasing mania symptoms, with effect sizes comparable to those found for antipsychotics in schizophrenia. Some of the antipsychotics may be more effective than lithium and valproate. Moreover, some mood stabilizers do prevent manic relapse. Pragmatic studies with head-to-head comparisons of several mood stabilizers seem to be particularly scarce.

In pregnancy, sodium valproate and carbamazepine are particularly problematic because of the high rates of associated malformations. Lithium and antipsychotics, especially some of the FGAs, seem to be much safer alternatives [Gentile, 2010, 2012]. The literature on the use of mood stabilizers in pregnancy is generally of lower methodological quality because RCTs are ethically not feasible. Moreover, the data are often derived from other populations than those with bipolar disorders, such as patients with epilepsy in the case of anticonvulsants, and in patients with hyperemesis gravidarum in the case of antipsychotics, which may confound the results. Finally, the latest systematic reviews are already a few years old. The question of which should be the first-line agent in this special situation seemingly remains to be finally resolved.

Conclusions

Antipsychotics, in particular some of the SGAs, seem to be drugs of first choice for both schizophrenia and bipolar mania. However, the available evidence for safety in pregnancy is thus far limited, particularly for the SGAs [Gentile, 2011]. The optimal use of antipsychotic drugs is often hampered by troublesome side effects. Traditionally the FGAs have been associated with EPS, whereas the SGAs are coupled to weight gain and metabolic adverse effects. Although the dichotomy still has some empirical basis, the latest evidence indicates a much more complex picture of both FGAs and SGAs being heterogeneous drug classes. This is reflected in recent updates of major schizophrenia treatment guidelines, as, whereas the SGAs were generally regarded as drugs of first choice following the first years of their introduction, principally because of their lower propensities for causing EPS, the newer guidelines do not recommend any particular drug or drug class over another in first-episode psychosis [Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011; Buchanan *et al.* 2010; Kuipers, 2009]. The latest evidence shows rather consistently that there are differences among individual antipsychotic agents, including differential efficacy and times until treatment discontinuation, but these differences have not yet made an impact on the treatment guidelines.

This prospective review has focused on mean effects and side effects of the drugs as reported in recent studies. However, the group means may not be particularly useful in disorders that are biologically heterogeneous and with large interindividual variations in drug response and tolerance, which is the case for schizophrenia and mania. Symptom profiles have been shown to predict neither efficacy nor tolerability of any particular drug in the individual patient [Manschreck and Boshes, 2007]. A clinically well known example is that of antipsychotic-induced weight gain. The mean difference among the SGAs is in the magnitude of a few kilograms but for individual patients the weight gain may be 10–20-fold the mean value. At least some of the variation can be attributed to different genetic profiles [Arranz and de Leon, 2007]. Although progress is being made in the area of pharmacogenetics, no major breakthrough has yet surfaced [Arranz *et al.* 2011]. Thus far the current evidence base offers guidance with regards to which drugs have the highest likelihood of a beneficial outcome in the drug-naïve patient, but also which adverse effects can be expected. More importantly, based on the individual response to any particular drug, the evidence base supplies valuable information on which drug to choose next in case of insufficient effect or intolerable side effects of the first drug as choosing a drug with a different profile would seem rational [Leucht *et al.* 2011b].

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