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REVIEW ARTICLE

A Review of the Pharmacology, Efficacy and Tolerability of Recently Approved and Upcoming Oral Antipsychotics: An Evidence-Based Medicine Approach

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Abstract Evidence-based medicine (EBM) is a broad concept, but the key elements include the incorporation of clinical judgment (which requires clinical experience) together with relevant scientific evidence while remaining mindful of the individual patient's values and preferences. Using the framework and philosophy of EBM, this systematic review summarizes the pharmacology, efficacy, and tolerability of newly approved oral antipsychotics, including iloperidone, asenapine, and lurasidone, and outlines what is known about agents that are in late-stage clinical development, such as cariprazine, brexpiprazole, zicronapine, bitopertin, and EVP-6124. Potential advantages and disadvantages of these agents over existing antipsychotics are outlined, centered on clinically relevant issues such as the potential for weight gain and metabolic abnormalities, potential association with somnolence/sedation, extrapyramidal side effects, akathisia, and prolongation of the electrocardiogram (ECG) QT interval, as well as practical issues regarding dosing instructions, titration requirements, and drug–drug interactions. Lurasidone appears to be best in class in terms of minimizing untoward alterations in body weight and metabolic variables. However, iloperidone, asenapine, lurasidone, and cariprazine differ among themselves in terms of on-label dosing frequency (once daily for lurasidone and, presumably, cariprazine versus twice daily for iloperidone and asenapine), the need for initial titration to a therapeutic dose for iloperidone and possibly cariprazine, requirement to be taken sublingually for asenapine, requirement for administration with food for lurasidone, lengthening of the ECG QT interval (greater for iloperidone than for asenapine and no effect observed with lurasidone), and adverse effects such as akathisia (seen with cariprazine, lurasidone, and asenapine but not with iloperidone) and sedation (most notable with asenapine).

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1 Introduction

Evidence-based medicine (EBM) is a broad concept, but the key elements include the incorporation of clinical judgment (which requires clinical experience) together with relevant scientific evidence while remaining mindful of the individual patient's values and preferences [1]. Sackett et al. [2] emphasized that the philosophy of EBM is driven by the desire to provide optimal patient-centered care and is clearly not "cookbook medicine." Figure 1 outlines a five-step process that makes explicit the EBM process [3].

The years 2009 to date have seen the introduction of three new oral second-generation antipsychotics in the USA, iloperidone (Fanapt®, Novartis) indicated for the treatment of schizophrenia, asenapine (Saphris®, Merck) indicated for the treatment of schizophrenia and for bipolar mania/mixed episodes, and lurasidone (Latuda®, Sunovion) indicated for the treatment of schizophrenia and, as of 2013, also for bipolar I depression. In late-stage clinical development (phase III) are additional medications that may prove to be helpful in the treatment of schizophrenia and/or bipolar disorder. These include two dopamine D2 receptor partial agonists, cariprazine (Forest) and brexpiprazole (Otsuka), and a dopamine D2 receptor antagonist, zicronapine (Lundbeck). Also in phase III are bitopertin (Roche/Genentech), a glycine transport inhibitor that may have antipsychotic effects, and EVP-6124 (EnVivo), an alpha-7 nicotinic acetylcholine receptor agonist being tested for its potential pro-cognitive effects. This article

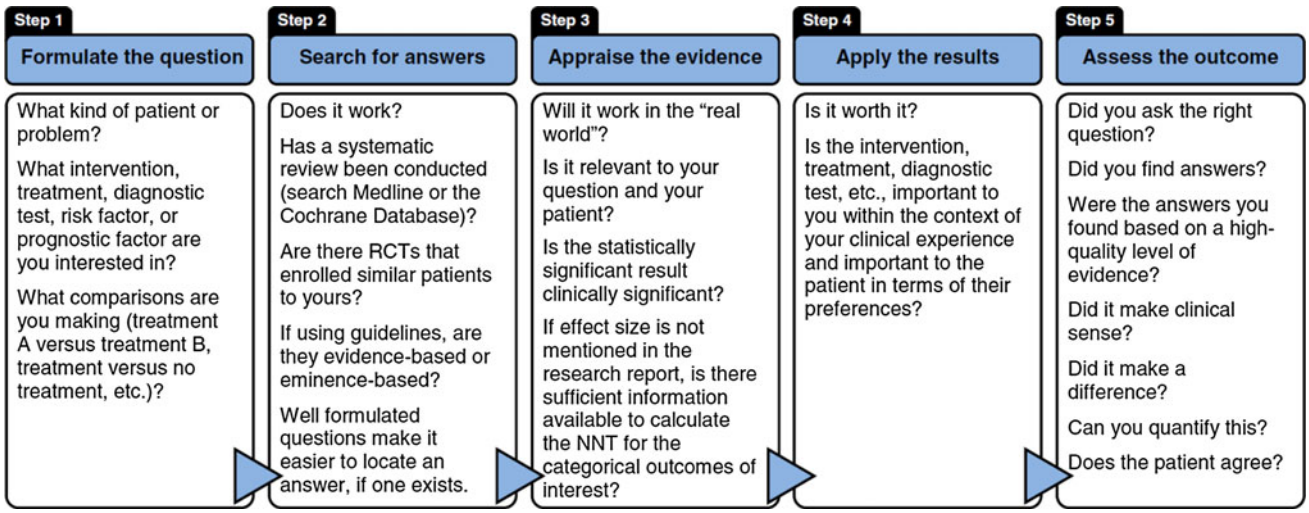

Fig. 1 The 5-step evidence-based medicine process (reproduced with permission from Citrome and Ketter [3]). *NNT* number needed to treat, *RCTs* randomized controlled trials

aims to apply the five-step process of EBM to the clinical problem of schizophrenia and asks the question "What is new or different about the new antipsychotics that would help treat my individual patient with schizophrenia?". Where applicable, data for the use of these agents for bipolar disorder are also considered. Agents that are not anticipated to be commercialized in the USA are not discussed.

Although the five-step EBM process is used as a framework, a complete discussion of EBM is beyond the scope of this review and the reader is referred to Box 1 for additional resources.

2 Box 1. Evidence-based medicine resources

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British Medical Journal Evidence-Based Medicine Online: http://ebm.bmj.com/.

Centre for Evidence-Based Medicine: http://ktclearinghouse.ca/cebm.

The Cochrane Collaboration: http://www.cochrane.org/.

Gray GE. Concise Guide to Evidence-Based Psychiatry. Washington, DC: American Psychiatric Publishing, Inc.; 2003.

Guyatt GH, Rennie D, Meade MO, Cook DJ. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Second edition. New York: McGraw-Hill Medical; 2008.

Guyatt GH, Rennie D, Meade MO, Cook DJ. Users' Guides to the Medical Literature: Essentials of Evidence-Based Clinical Practice. Second Edition. New York: McGraw-Hill Medical; 2008.

Straus SE, Glasziou P, Richardson WS, Haynes RB. Evidence-Based Medicine: How to Practice and Teach EBM. Fourth edition. Edinburgh: Churchill Livingstone; 2010.

3 Formulating the Question

3.1 "What is New or Different about the New Antipsychotics that Would Help Treat My Individual Patient with Schizophrenia?"

Despite the number of different antipsychotics commercially available, schizophrenia remains a complex and difficult disorder to treat. In clinical practice, the heterogeneity in individual patient response in terms of both efficacy and tolerability to different agents is at times astonishing. This leads to the common practice of switching medications, one after the other, in order to find the best fit and where adherence can be maximized. The research evidence supports the notion that the different antipsychotics each have their own 'personalities', and these different profiles are used as a first step in medication selection [4], but there is never any guarantee that any choice will be a successful one. Finding the 'perfect' medication is elusive and thus new treatments are often eagerly anticipated. Issues that require consideration include the type of patient that would potentially benefit from the intervention (diagnosis, specific symptom profile, stage of the illness, etc.), the anticipated robustness of the treatment effect (magnitude and durability of symptom reduction, effects on functionality), commonly encountered adverse events and safety concerns (such as the potential for weight gain and metabolic abnormalities, potential association with sedation, extra-pyramidal side effects, akathisia, and prolongation of the ECG QT interval), and logistical concerns such as when and how often the agent needs to be administered and if there are any special instructions for how the medicine needs to be taken (such as with food or without food), whether titration to a

therapeutic dose is required, whether there are any special monitoring requirements, and the potential for drug–drug interactions.

3.2 "When does a Difference Make a Difference?"

When assessing whether or not a statistically significant treatment difference observed in a clinical trial is clinically relevant, the effect size will need to be considered. Number needed to treat (NNT), and its counterpart, number needed to harm (NNH), are clinically intuitive effect size measures that help judge the clinical significance of a statistically significant result [5, 6]. NNT and NNH are also simpler for the average clinician to calculate 'on-the-fly' than other effect size measures [5]. NNT answers the question 'How many patients would you need to treat with intervention A instead of intervention B before you would expect to encounter one additional positive outcome of interest?' [6]. NNH answers the question 'How many patients would you need to treat with intervention A instead of intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?' [6]. In general, 'single-digit' NNT values are desired, with lower numbers representing more robust effect size differences for the efficacy outcomes. However, 'double-digit' or larger NNH values are desired, with the consequence that undesirable safety or tolerability outcomes will be less frequently encountered [6].

The ratio of NNH : NNT, known as the likelihood to be helped or harmed (LHH), can further illustrate trade-offs between benefits and harms [6]. For example, for a hypothetical medication, if the NNT versus placebo is 4 for a clinically relevant therapeutic response and the NNH versus placebo for persistent tremor is 6, LHH is 6/4 or 1.5. This LHH of 1.5 for response versus persistent tremor can be interpreted as 'treatment was 1.5 times more likely to help (therapeutic response) than harm (tremor) the patient.' An LHH much greater than 1 is the norm when comparing a desired outcome, for example, robust response versus a severe adverse event. An LHH a little greater than 1 is usually observed for acceptable interventions when comparing a desired outcome with an adverse event that is usually mild or moderate but that may still lead to discontinuation. LHH less than or equal to 1 is usually only acceptable when comparing a desired outcome with an adverse event that is usually mild or moderate but that is usually temporary and does not lead to discontinuation, or there is a particularly urgent need for benefit (efficacy) that mitigates an otherwise prohibitive risk of harm (side effects) [6].

A caveat is that NNT, NNH, and LHH are tools intended for the clinician, and not the statistician. Although NNT measures outcomes in 'patient units' compared with commonly reported continuous metrics (such as changes in rating scale score), some precision is lost and NNT would not be suitable as a primary outcome measure when reporting a clinical trial. A more complete discussion of NNT with several examples can be found elsewhere [5, 6].

4 Searching for Answers

A literature search of the US National Library of Medicine's PubMed database on 7 April 2013 for the text words 'iloperidone,' 'asenapine,' 'lurasidone,' 'cariprazine,' 'brexpiprazole,' 'zicronapine,' 'bitopertin,' and 'EVP-6124' produced 112, 150, 83, 19, 0, 0, 9, and 1 record(s), respectively. Of these, 26 were primary or first reports of relevant clinical trials and their extensions (if applicable), excluding studies that were primarily drug interaction/pharmacokinetic or dedicated cardiac QT trials [7–32]. Two relevant meta-analyses were also found: one for asenapine for the treatment of schizophrenia [33] and one that included several of the new agents regarding effects on body weight and metabolic adverse effects [34]. Several systematic and narrative reviews were found, and these provided additional information extracted from regulatory documents and meeting abstracts (and whose references often included other meeting abstracts). Of these systematic and narrative reviews, the works created by the present author [35–52], including pooled analyses of available clinical trials [40, 43, 44], were used as a basis for much of the material presented here, and updated where possible; other systematic reviews found did not generally quantify effect sizes using NNT or NNH. The US product labels for iloperidone [53], asenapine [54], and lurasidone [55] provided additional information. For zicronapine and EVP-6124, agents for which scant information was found, a repeat search was made using EMBASE for abstracts of presentations made at conferences, yielding 0 and 1 relevant records [56], respectively. In view of the lack of clinical data regarding zicronapine found, a search was made regarding investor-oriented press releases by the manufacturer and a summary of phase II trials was found [57].

In addition, a search of the clinical trial registry clinicaltrials.gov on 7 April 2013 for the text words 'iloperidone,' 'asenapine,' 'lurasidone,' 'cariprazine,' 'brexpiprazole,' 'zicronapine,' 'bitopertin,' and 'EVP-6124' produced 11, 47, 41, 16, 9, 4, 7, and 9 records, respectively. For agents not yet commercially available but whose formal nomenclature has been established, an additional search on clinicaltrials.gov was conducted using their preliminary designations (RGH-188 for cariprazine, OPC-34712 for brexpiprazole, Lu 31-130 for zicronapine, and RO4917838 for bitopertin); this search yielded 12, 20, 4, and 21 records, respectively.

Whenever available, categorical outcomes were preferred when describing results. If NNT or NNH values were not reported for these outcomes, they were then calculated using the data provided. When 95 % confidence intervals (CI) were not reported, they were calculated by the author. When the 95 % CI encompassed 'infinity,' meaning that the NNT or NNH estimate was not statistically significant, the notation 'ns' is made.

5 Appraising the Evidence

Published are primary reports of several short- and longer-term randomized controlled trials of iloperidone [7–11], asenapine [12–22], and lurasidone [23–32]. Reviews of cariprazine summarize short-term studies [36–38]. Very limited information is available for brexpiprazole, zicronapine, bitopertin, and EVP-6124. In general, studies have recruited individuals who have been ill for, on average, several years. Persons with active co-morbid alcohol or substance use disorders are generally excluded, as are patients who have not responded to prior treatments and considered to be possibly treatment resistant. These reasons for exclusion are understandable, as they can potentially interfere with obtaining or even assessing treatment response. For safety reasons, individuals with medically relevant comorbid somatic conditions are also ineligible to participate, as are patients who are suicidal or considered a danger to others. Although all of these criteria for exclusion result in a study sample that may be dissimilar to patients treated in the 'real world,' the expectation is that it is possible to generalize results of the clinical trials to clinical practice. For the acute studies in subjects with schizophrenia, the primary outcome measure was generally either the Brief Psychiatric Rating Scale (BPRS) total score or the Positive and Negative Syndrome Scale (PANSS) total score. For the acute studies in subjects with bipolar mania/mixed episodes, the primary outcome measure was generally the Young Mania Rating Scale (YMRS) score.

5.1 Iloperidone

5.1.1 Pharmacodynamics and Pharmacokinetics

Table 1 outlines the principal pharmacodynamic and pharmacokinetic attributes of iloperidone. Of clinical and practical importance is the relatively high affinity for noradrenergic alpha 1 receptors (K_i 0.36 nM), compared with the affinity for serotonin 5-HT2A and dopamine D2 receptors (K_i 5.6 and 6.3 nM, respectively). This is the explanation for iloperidone's potential for dizziness and orthostatic hypotension and this potent effect at noradrenergic alpha 1 receptors is the principal reason for the requirement that iloperidone be titrated to its therapeutic target dose range of 12–24 mg/day. The randomized controlled trials of iloperidone (Table 2) tested several doses of iloperidone versus placebo, and all employed twice-daily (bid) dosing, explaining why the product label recommends this as the dose frequency, even though the elimination half-life approximates 24 h, which would possibly justify once-daily dosing once titration to a tolerable dose has taken place. An open-label extension study did suggest that 12 mg given once daily at bedtime was efficacious and tolerable [11].

Other receptor-binding characteristics may be important clinically. Low affinity to muscarinic receptors would theoretically predict a low propensity for causing anticholinergic side effects, including cognitive dysfunction and gastrointestinal disturbances, at clinically relevant doses [58]. Low affinity to histamine H1 receptors would theoretically predict a low propensity for causing sedation or weight gain [58]. However, proof that these receptor-binding affinities are clinically relevant in the day-to-day treatment of patients requires the conduct of clinical trials to test these hypothesized effects.

5.1.2 Efficacy

Four short-term, double-blind, placebo- and active-controlled efficacy studies were conducted [7–9]. Three were 6 weeks in duration and one was 4 weeks in duration. Two studies were accepted by the US FDA as supportive of iloperidone's efficacy in the acute treatment of schizophrenia in adults, although there was disagreement between the manufacturer and the FDA as to which two studies were considered positive [50]. A patient-level meta-analytic post hoc analysis of pooled patient data from all four trials demonstrated superiority of iloperidone over placebo on the PANSS total, PANSS positive subscale, PANSS negative subscale, and BPRS-derived (BPRSd) total scores [43], and on the PANSS factor scores [44]. Effect sizes for iloperidone when dosed in the therapeutic range were similar to those observed for ziprasidone and haloperidol but somewhat lower than those observed for risperidone. The latter difference was attenuated when subjects who have been treated for less than 2 weeks were excluded; thus, this difference from risperidone may be potentially explained by the design of the clinical trials where iloperidone was titrated to a therapeutic dose more slowly than for risperidone. Another possible explanation is that risperidone is superior in efficacy to iloperidone (and also to ziprasidone and haloperidol), which would be consistent with a series of meta-analyses by Leucht et al. [59–61], demonstrating that clozapine, olanzapine, amisulpride, and risperidone have efficacy advantages over other first- and second-generation antipsychotics.

Table 1 Overview and characteristics of iloperidone, asenapine, lurasidone, and cariprazine

	Iloperidone	Asenapine	Lurasidone	Cariprazine
US brand name	Fanapt®	Saphris®	Latuda®	Pending
Marketed in USA by	Novartis	Merck	Sunovion	Forest
Date of initial US approval	6 May 2009	14 Aug 2009	28 Oct 2010	Anticipated 2013
US patent expiration	2016	2020	2018	Estimated 2027
Approved indications	Schizophrenia	Schizophrenia; acute tx of manic or mixed episodes associated with BDI as monotherapy or adjunctive therapy with either Li or VAL	Schizophrenia; depressive episodes associated with BDI (bipolar depression), as monotherapy and as adjunctive therapy with Li or VAL	Initial submission for schizophrenia and acute tx for manic or mixed episodes associated with BDI
Other indications in phase III as per clinicaltrials.gov				Adjunctive use for major depressive disorder
Target dose	12–24 mg/day	Acute tx: 10 mg/day for schizophrenia and 20 mg/day for bipolar mania or mixed episodes	40–160 mg/day (schizophrenia); 20–120 mg/day (bipolar depression)	Pending
Dose frequency	Twice daily	Twice daily	Once daily	Once daily
Titration to therapeutic dose required?	Yes (4 days)	No	No	Likely
Dose administration	Oral, with or without food	Sublingual, no food or liquid for 10 min after administration	Oral, in the presence of ≥350 calories of food	Oral, with or without food
Strengths available	1, 2, 4, 6, 8, 10, and 12 mg	5 and 10 mg (two flavors available, including black cherry)	20, 40, 60, 80, and 120 mg	Pending
Pharmacodynamics (K_i in nM)				
Affinity K_i <0.1		5-HT2C (0.03), 5-HT2A (0.06)		D3 (0.085)
K_i ≥0.1 and <1	NE Alpha 1 (0.36)	5-HT7 (0.13), 5-HT2B (0.16), 5-HT6 (0.25), D3 (0.42)	5-HT2A (0.47), 5-HT7 (0.495), D2 (0.994)	D2L (0.49), D2S (0.69), 5-HT2B (0.58)
K_i ≥1 and <10	5-HT2A (5.6), D2 (6.3), D3 (7.1)	H1 (1.0), D4 (1.1), NE Alpha 1 (1.2), NE Alpha 2 (1.2), D2 (1.3), D1 (1.4), 5-HT5 (1.6), 5-HT1A (2.5), 5-HT1B (4.0), H2 (6.2)	5-HT1A (6.38)	5-HT1A (3)
K_i ≥10 and <100	5-HT7 (22), D4 (25), 5-HT6 (43)		NE alpha 2C (10.8), NE alpha 2A (40.7)	5-HT2A (19), H1 (23)
K_i ≥100 and <1,000	5-HT1A (168), D1 (216), H1 (473)			5-HT7 (111), 5-HT2C (134)
K_i ≥1,000	Muscarinic	Muscarinic M1	H1 and muscarinic M1	
Receptor functionality	Antagonist at D2, D3, 5-HT1A, and NE alpha1 and alpha2C	Antagonist at the above receptors	Antagonist at the above receptors, except for 5-HT1A, where activity is that of partial agonism	Antagonist at the above receptors, except for D3, D2L, D2S, and 5-HT1A, where activity is that of partial agonism

Table 1 continued

	Iloperidone	Asenapine	Lurasidone	Cariprazine
Pharmacokinetics				
Time to peak plasma concentration	2–4 h	0.5–1.5 h	1–3 h	3–4 h
Elimination half-life	CYP2D6 extensive metabolizers: 18 h (23–26 for metabolites); CYP2D6 poor metabolizers: 33 h (31–37 for metabolites)	24 h	18 h (at 40 mg/day)	2–5 days
Protein-bound	95 %	95 %	99 %	Pending
Route of metabolism	CYP2D6 and CYP3A4	UGT1A4 and CYP1A2	CYP3A4	CYP3A4 and CYP2D6
Important metabolites	P88 (in equilibrium; crosses the BBB), P95 (does not cross the BBB)	Asenapine activity is primarily due to the parent drug	Two active metabolites with shorter half-lives than the parent compound	Desmethylcariprazine and didesmethyl-cariprazine, the latter's half-life is substantially longer than that for cariprazine (2–3 weeks)
Drug–drug interactions?	Inhibitors of CYP3A4 (e.g. ketoconazole) or CYP2D6 (e.g. fluoxetine, paroxetine) can inhibit elimination and cause increased blood levels of iloperidone twofold; because of the NE alpha 1 receptor antagonism, can add to the effect of certain antihypertensive agents	Coadminister with caution with fluvoxamine (CYP1A2 inhibitor); because of the NE alpha 1 receptor antagonism, can add to the effect of certain antihypertensive agents; asenapine can inhibit CYP2D6, resulting in twofold increases in paroxetine concentrations	Co-administration with drugs that are strong inhibitors of CYP3A4 (such as ketoconazole), or strong inducers (such as rifampin) is contraindicated; lurasidone should be initiated at 20 mg/day and not exceed 80 mg/day if coadministered with a moderate CYP3A4 inhibitor (such as diltiazem)	Pending
Dosage adjustment in renal impairment?	None	None	Start at 20 mg/day and do not exceed 80 mg/day in patients with moderate and severe renal impairment	Pending
Dosage adjustment in liver impairment?	Iloperidone is not recommended in patients with hepatic impairment	Asenapine is not recommended in patients with severe hepatic impairment	Start at 20 mg/day and do not exceed 40 mg/day in patients with severe hepatic impairment or 80 mg/day in patients with moderate hepatic impairment	Pending

From US product labeling [53–55] and a review of cariprazine [38]

BBB blood–brain barrier, *BDI* bipolar I disorder, *CYP* cytochrome P450, *Li* lithium, *tx* treatment, *VAL* valproate

Data permitting the calculation of NNT for response versus placebo are limited to one trial [7], where using a threshold of a ≥20 % decrease from baseline on the PANSS positive subscale, significantly more patients receiving iloperidone (72 %) than placebo (52 %) met this criterion, yielding an NNT of 5 (95 % CI 4–13) [52]. The corresponding information for ziprasidone was not reported [7].

Efficacy data from 52-week, double-blind trials are available [10]. Data were pooled from these three prospective multicenter studies comparing iloperidone 4–16 mg/day with haloperidol 5–20 mg/day. Each study was identically designed, with a 6-week stabilization period followed by a 46-week double-blind maintenance period. There was no placebo arm. Rates of relapse and reasons for relapse were similar between iloperidone and haloperidol. However, the FDA did not accept these studies as supportive for iloperidone because of issues surrounding the non-inferiority design [50]. A more traditional relapse-prevention study of iloperidone versus placebo is underway (NCT01291511).

Table 2 Completed iloperidone double-blind, randomized, controlled trials for which results are available

Study	Duration (weeks)	Disease state	N randomized	ILO dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
Cutler et al. [7]	4	SCZ, acute exacerbation	593	24 mg/day (295)	ZIP 160 mg/day (149)	149	ILO statistically significantly superior to PL, as was the active control. A 25-week ol extension trial has been published [11]
Potkin et al. [8] (Study 1)	6	SCZ or SAD, acute or subacute exacerbation	621	4 mg/day (121), 8 mg/day (125), 12 mg/day (124)	HAL 15 mg/day (124)	127	When only pts with SCZ were included,[b] the active control separated statistically from PL, but the ILO 8 and 12 mg/day combined group did not (this was the pre-specified primary test); the 12 mg/day dose by itself may be therapeutic
Potkin et al. [8] (Study 2)	6	SCZ or SAD, acute or subacute exacerbation	616	4–8 mg/day (153), 10–16 mg/day (154)	RIS 4–8 mg/day (153)	156	When only pts with SCZ were included,[b] the ILO versus PL comparisons were nonsignificant. Active control arm was statistically significantly superior to PL and ILO
Potkin et al. [8] (Study 3)	6	SCZ or SAD, acute or subacute exacerbation	706	12–16 mg/day (244), 20–24 mg/day (145)	RIS 6–8 mg/day (157)	160	When only pts with SCZ were included,[b] ILO and active control separated statistically from PL
Kane et al. [10]	52	SCZ or SAD	489; see comments	4–16 mg/day (371); mean dose 12.5 mg/day	HAL 5–20 mg/day (118); mean dose 12.5 mg/day	NA	Three 52-week studies were pooled and analyzed with a non-inferiority design. 1,644 randomized in the initial 6-week db phase (ILO 1,239, HAL 405), and 1,014 (81.8 %) pts receiving ILO and 312 (77.0 %) receiving HAL completed this phase. Of these, 371 (36.6 %) in the ILO group and 118 (37.8 %) in the HAL group exhibited a tx response and were eligible to enter the 46-week db maintenance phase and to be included in this analysis. 473 (ILO 359, HAL 114) were included in the long-term efficacy analysis; 489 (ILO 371, HAL 118) in the safety analysis. Rates of and reasons for relapse were similar between the two groups

[a] Outcomes based on the Brief Psychiatric Rating Scale and/or Positive and Negative Syndrome Scale, unless otherwise noted

[b] i.e. excluding patients with SAD

db double-blind, *HAL* haloperidol, *ILO* iloperidone, *ol* open-label, *PL* placebo, *pts* patients, *RIS* risperidone, *SAD* schizoaffective disorder, *SCZ* schizophrenia, *tx* treatment, *ZIP* ziprasidone

5.1.3 Tolerability and Safety

Commonly observed adverse reactions in short-term trials (incidence ≥5 % and twofold greater than placebo) were dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase [53]. The rates and NNH versus placebo for these are summarized in Table 3. Dizziness and tachycardia were more common with iloperidone 20–24 versus 10–16 mg/day in the clinical trials; however, this may not necessarily translate to what can be expected in clinical practice as patients in the clinic would not be routinely force-titrated to a high dose. In general, for all therapeutic agents, it is important to remember that these adverse event rates are from spontaneously reported events occurring during the conduct of the clinical trial. They were not specifically elicited from the participants in the trial, in contrast to how a clinician might inquire explicitly about whether or not their patient is experiencing any adverse reactions such as dizziness. Thus, rates in clinical practice for some events may be higher than what is reported in a registration trial.

The non-specific complaint of 'weight increased' requires further explanation, as the incidence at the higher dose range (20–24 mg/day) was 9 % in contrast to the lower dose range and for placebo where incidence was 1 %; this contrast of 9 versus 1 % is potentially misleading as the amount of weight gained is not taken into account. Mean weight change from baseline to endpoint in the 4- to 6-week short-term studies was 2.0 kg for patients receiving iloperidone 10–16 mg/day, 2.7 kg with iloperidone 20–24 mg/day, and −0.1 kg with placebo [53]. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg [53]. However, a more clinically relevant metric is the incidence of gaining ≥7 % of body weight from baseline during the course of the short-term (4–6 weeks) clinical trials. This amount of weight gain occurred in 4 % of subjects randomized to placebo and in 12 and 18 % of subjects randomized to iloperidone 10–16 mg/day and 20–24 mg/day, respectively, yielding NNH values versus placebo of 13 (95 % CI 9–22) and 8 (95 % CI 6–11), respectively. Pooling the data for doses of iloperidone 10–24 mg/day, NNH versus placebo for weight gain ≥7 % is 10 (95 % CI 8–13). Product labeling notes that no medically important differences were observed between iloperidone and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry, including glucose, triglycerides, and total cholesterol measurements [53]. Shifts to abnormal ranges for metabolic variables are reported in product labeling for the 24 mg/day dose, for which fasting bloods were obtained in the 4-week study [7, 53]. These are summarized in Table 4. Interpretation of these numbers should be made with caution as these are from a single study at the highest recommended dose of iloperidone and the sample sizes were relatively small compared with the overall safety database. Of note, the direction of harm for the shift from normal to abnormal for low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol is in favor of iloperidone, representing a 'negative' NNH. Longer-term data extending out to over 12 months are supportive of iloperidone's relatively benign metabolic profile [53].

The product label for iloperidone contains similar language as for ziprasidone regarding potential prolongation of the ECG QT interval [62, 63]. Increases in corrected QT (QTc) were observed with all dose ranges of iloperidone; however, there were no deaths or serious arrhythmias attributable to QT prolongation in these studies [53]. In the 52-week trials, mean changes in the ECG QTc interval were 10.3 ms for iloperidone and 9.4 ms for haloperidol at endpoint [10]. In a dedicated QT study [64], 188 adults with schizophrenia or schizoaffective disorder and normal

Table 3 Iloperidone: incidence and number needed to harm (95 % CI) versus placebo for treatment-emergent adverse events as reported in product labeling for events with incidence ≥5 % and twofold greater than placebo in acute studies (adapted with permission from Citrome [52])

Adverse event	Placebo ($N = 587$)	Iloperidone 10–16 mg/day ($N = 483$)		Iloperidone 20–24 mg/day ($N = 391$)	
	Incidence (%)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)
Dizziness	7	10	34 (ns)	20	8 (6–12)
Somnolence	5	9	25 (15–112)	15	10 (8–17)
Tachycardia	1	3	50 (27–359)	12	10 (7–13)
Dry mouth	1	8	15 (11–23)	10	12 (9–17)
Weight increased	1	1	No difference	9	13 (10–20)
Nasal congestion	2	5	34 (19–134)	8	17 (12–33)
Fatigue	3	4	100 (ns)	6	34 (18–369)
Orthostatic hypotension	1	3	50 (27–359)	5	25 (16–59)

CI confidence interval, *NNH* number needed to harm

ns not statistically significant (the 95 % CI encompasses infinity)

Table 4 Iloperidone: incidence of shifts from the normal to abnormal range for metabolic variables (fasting) and number needed to harm (95 % CI) versus placebo

Metabolic variable	Placebo	Iloperidone 24 mg/day	
	Incidence (%)	Incidence (%)	NNH (95 % CI)
Serum glucose normal to high (<100 to ≥126 mg/dL)	2/80 (2.5)	18/169 (10.7)	13 (8–43)
Total cholesterol normal to high (<200 to ≥240 mg/dL)	1/72 (1.4)	5/141 (3.6)	47 (ns)
LDL cholesterol normal to high (<100 to ≥160 mg/dL)	1/42 (24)	1/90 (1.1)	−79 (ns)
HDL cholesterol normal to low (≥40 to <40 mg/dL)	19/80 (23.8)	20/166 (12.1)	−9 (−5 to −88)
Triglycerides normal to high (<150 to ≥200 mg/dL)	6/72 (8.3)	15/148 (10.1)	56 (ns)

Data from the product label [53]

CI confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NNH* number needed to harm

ns not statistically significant (the 95 % CI encompasses infinity)

ECGs at baseline were randomized to iloperidone 8 mg bid, 12 mg bid, or 24 mg once daily; quetiapine 375 mg bid; or ziprasidone 80 mg bid. Iloperidone bid produced mean changes in the Fridericia QTc interval (QTcF) similar to those produced by ziprasidone (8.5–9.0 versus 9.6 ms, respectively) and higher than those produced by quetiapine (1.3 ms). Iloperidone 24 mg once daily produced a mean QTcF change of 15.4 ms. Coadministration of metabolic inhibitors with iloperidone resulted in greater increases in the QTc interval. No patients experienced QTc ≥500 ms.

Product labeling notes that in the short-term trials, iloperidone was associated with modest levels of prolactin elevation compared with greater prolactin elevations observed with some other antipsychotic agents [53]. In the three 6-week trials [8, 9], prolactin levels were generally decreased after treatment with all iloperidone dosages for which this information was available and with placebo, but were significantly increased with both haloperidol and risperidone [52]. In the 4-week study [7], there was a small increase in mean change from baseline to endpoint in plasma prolactin levels of 2.6 ng/mL for iloperidone 24 mg/day. In this trial, elevated plasma prolactin levels were observed in 26 % of adults treated with iloperidone compared with 12 % in the placebo group [53], for an NNH of 8 (95 % CI 5–15). The study report [7] notes that 14.8, 9.5, and 1.5 % of subjects receiving iloperidone, ziprasidone, and placebo, respectively, had prolactin values outside the upper extended reference range (actual range not defined) (NNH versus placebo 8 [95 % 6–12] and 13 [95 % CI 9–23] for iloperidone and ziprasidone, respectively).

There was no significant association with extrapyramidal disorder, akathisia, or tremor noted for iloperidone at any dose.

5.1.4 Summary of Clinical Utility

At present, the sole NNT value available is for response versus placebo from the clinical trial where iloperidone 24 mg/day was compared with placebo, with ziprasidone serving as an active control [7]. Using a threshold of a ≥20 % decrease from baseline on the PANSS positive subscale as the desired outcome, the NNT was 5 (95 % CI 4–13). The dose range of 10–16 mg/day does not appear to be substantially different than the dose range of 20–24 mg/day when comparing groups on reduction of psychopathology [43]. When calculating the LHH and contrasting an NNT of 5 for efficacy with the NNH for adverse outcomes across the therapeutic dose range, the LHH was >>1 for extrapyramidal side effects or akathisia, 1.6–2.6 for weight gain ≥7 % within 4–6 weeks, and 2.0–5.0 for somnolence.

Although there is a warning regarding the potential for prolongation of the ECG QT profile, a more pragmatic obstacle to using iloperidone is the requirement for titration to the therapeutic dose range of 12–24 mg/day (in order to manage the risk of orthostatic hypotension). This is not ordinarily an issue when switching antipsychotics where the cross-tapering period may be ≥4 days, but can be problematic when rapid control of psychotic symptoms is required when initiating an antipsychotic, especially in an agitated individual. Nonetheless, iloperidone's modestly benign weight and metabolic profile, combined with its neutrality regarding extrapyramidal side effects or akathisia, renders iloperidone as a useful addition to the psychiatric armamentarium.

5.2 Asenapine

5.2.1 Pharmacodynamics and Pharmacokinetics

Asenapine, available as an orally disintegrating tablet administered sublingually, differs from other oral antipsychotics in that it is absorbed through the oral mucosa. This is in direct contrast to orally disintegrating tablets of olanzapine, risperidone, and aripiprazole, all of which must be swallowed in order to be effective. Asenapine, if swallowed, has a bioavailability of <2 % [51, 65, 66].

Although the asenapine tablet disintegrates within seconds, and thus is not easy to swallow, it is recommended that drinking as well as eating should be avoided for 10 min after administration [54]. However, waiting the full 10 min may not be necessary; the mean asenapine exposure for subjects given water at 2 min was only ~20 % lower and at 5 min was only ~10 % lower [66]. This reduction of availability by 10–20 % may not be clinically relevant, as these differences in exposure are actually smaller than the overall variability observed in studies, where maximum concentration and overall exposure varied 45 and 37 %, respectively (with mean inter-individual variability 33 and 26 %, respectively, and mean intra-individual variability 30 and 26 %, respectively) [65].

Asenapine has substantially higher affinity (K_i in nM) to serotonin 5-HT2C (0.03), 5-HT2A (0.06), 5-HT7 (0.13), 5-HT2B (0.16), 5-HT6 (0.25), and dopamine D3 (0.42) receptors than to dopamine D2 receptors (1.3) (see Table 1). Binding affinity to histamine H1 (1.0), dopamine D4 (1.1), norepinephrine alpha 1 (1.2), and norepinephrine alpha 2 (1.2) receptors approximates that for dopamine D2 receptors. Low affinity to muscarinic receptors would theoretically predict a low propensity for causing anticholinergic side effects. The remaining complex pharmacodynamic profile of asenapine is of potential interest, particularly for the serotonin 5-HT7 receptor where there are pre-clinical findings of a possible pro-cognitive effect [67]. Antagonism at serotonin 5-HT2C receptors can also theoretically be expected to produce desirable clinical effects, including improvements in both cognition and mood [58].

No initial dose titration to a therapeutic dose is necessary. The product label recommends specific target doses depending on the disease state and other circumstances for treatment: acute schizophrenia 5 mg bid, maintenance 10 mg bid, bipolar mania/mixed as a monotherapy 10 mg bid, bipolar mania/mixed with lithium or valproate 5 mg bid [54]. Doses may still be adjusted to 5 or 10 mg bid as needed. These doses and their frequency of administration are based on the design of the clinical trials used to obtain regulatory approval. However, the elimination half-life of asenapine is 24 h, suggesting that once-daily dosing may be appropriate. A study to examine once-daily dosing has been registered (NCT01549041). The time to maximum concentration for asenapine after dose administration is relatively brief (30–90 min), a property that has been exploited in a clinical trial testing asenapine for agitation (NCT01400113).

5.2.2 *Efficacy*

Short-term efficacy for schizophrenia was tested in four pivotal 6-week randomized, double-blind, placebo- and active comparator-controlled trials (Table 5). Two studies were accepted by the FDA as supportive of asenapine's efficacy in the acute treatment of schizophrenia in adults [12, 13]. There was one negative study where neither of the tested doses of asenapine statistically separated from placebo but the active control (olanzapine) did [51, 65]. There was one failed study where neither asenapine nor olanzapine separated from placebo [51, 65]. In one of the positive studies [12], asenapine was superior to placebo but the active control (risperidone) was not. A patient-level meta-analytic post hoc analysis of pooled patient data from all four trials was conducted and the asenapine treatment effects were further contrasted with those for other antipsychotics by adding the integrated asenapine data to previously completed meta-analyses [33]. Overall, asenapine was superior to placebo with regard to mean change in PANSS total score with an effect comparable to active controls from the same trials. In the network meta-analysis, asenapine ranked fourth among the eight agents in this analysis; the efficacy of asenapine was comparable to that of other second-generation antipsychotics; with estimated differences ranging from 3.9 points greater than ziprasidone to 2.9 points less than olanzapine.

Data for the calculation of NNT for response versus placebo are available for the two 6-week trials considered supportive for asenapine for schizophrenia. For one trial [12], using the threshold of a PANSS score reduction ≥20 % to define treatment response, 53 % of the patients in the asenapine group were responders, compared with 50 % in the risperidone group and 35 % in the placebo group (NNT asenapine versus placebo = 6, 95 % CI 3–121; NNT risperidone versus placebo = 7, ns) [51]. Using the criterion of a PANSS score reduction ≥30, 38 % of the patients in the asenapine group were responders, compared with 39 % in the risperidone group and 25 % in the placebo group (NNT asenapine versus placebo = 8, ns; NNT risperidone versus placebo = 7, ns) [51]. For the second study [13], responder analysis using the Clinical Global Impression-Improvement (CGI-I) score (response defined as a score of 1 or 2, i.e., "very much improved" or "much improved," respectively), revealed response rates of 48 % for asenapine 5 mg bid, 44 % for asenapine 10 mg bid, 44 % for haloperidol and 34 % for placebo (NNT asenapine 5 mg bid versus placebo = 8 [95 % CI 4–66]; NNT asenapine 10 mg bid versus placebo = 10; ns); NNT haloperidol versus placebo = 10; ns) [51]. Response defined as a ≥30 % reduction on the PANSS total score evidenced rates of 55, 49, 43, and 33 %, for asenapine 5 mg bid, asenapine 10 mg bid, haloperidol, and placebo, respectively, yielding an NNT of 5 (95 % CI 3–11), 7 (95 % CI 4–31), and 10 (ns) versus placebo for asenapine 5 mg bid, asenapine 10 mg bid, and haloperidol, respectively [45].

Table 5 Completed asenapine double-blind randomized controlled trials for which results are available

Study	Duration (weeks)	Disease state	N Randomized	ASE dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
Potkin et al. [12]	6	Schizophrenia, acute exacerbation	182	10 mg/day (60)	RIS 6 mg/day (60)	62	ASE 10 mg/day, but not active control, statistically separated from PL
See review, Citrome [51]	6	Schizophrenia, acute exacerbation	417	10 mg/day (106), 20 mg/day (102)	OLA 15 mg/day (103)	106	None of the ASE dose arms statistically separated from PL but active control did
See review, Citrome [51]	6	Schizophrenia, acute exacerbation	277	10 or 20 mg/day (91)	OLA 10–20 mg/day (93)	93	Neither ASE nor active control statistically separated from PL
Kane et al. [13]	6	Schizophrenia, acute exacerbation	458	10 mg/day (114), 20 mg/day (106)	HAL 8 mg/day (115)	123	ASE 10 mg/day and active control, but not ASE 20 mg/day, statistically separated from PL
Kane et al. [14]	26	Schizophrenia	386	10 or 20 mg/day (194); modal dose 20 mg/day	None	192	Incidence of relapse was significantly lower, and times to relapse and discontinuation were longer with ASE versus PL
Schoemaker et al. [15]	52	Schizophrenia or schizoaffective disorder	1,225	10 or 20 mg/day (913); mean dose 13.5 mg/day	OLA 10–20 mg/day (312); mean dose 13.6 mg/day	None	Psychopathological rating scale scores improved with both agents; the improvement was greater with OLA than with ASE using LOCF but not in an observed case analysis. Completers were eligible to continue into an extension study [16]
Buchanan et al. [17] (Study 1 - EH)	26	Schizophrenia with persistent negative symptoms	481	10 or 20 mg/day (241); mean dose 14.4 mg/day (15.9 mg/day in extension study)	OLA 10–20 mg/day (240); mean dose 12.5 mg/day (12.8 mg/day in extension study)	None	Completers were eligible to enter a 26-week extension study. ASE was not superior to OLA in change in the 16-item NSA scale total score in either the core study or the extension study. OLA was associated with modest, but significantly greater, changes in PANSS positive subscale score at various assessment times in the core study
Buchanan et al. [17] (Study 2 - WH)	26	Schizophrenia with persistent negative symptoms	468	10 or 20 mg/day (244); mean dose 14.5 mg/day (16.0 mg/day in the extension study)	OLA 10–20 mg/day (224); mean dose 14.0 mg/day (14.8 mg/day in the extension study)	None	Completers were eligible to enter a 26-week extension study. ASE was not superior to OLA in change in the 16-item NSA scale total score in the core study, but ASE was superior to OLA at week 52 in the extension study. OLA was associated with modest, but significantly greater, changes in PANSS positive subscale score at various assessment times in both the core and the extension study

Table 5 continued

Study	Duration (weeks)	Disease state	N Randomized	ASE dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
McIntyre et al. [18]	3	Manic or mixed episode, bipolar I disorder	489	Initiated at 20 mg/day, then 10 or 20 mg/day (194); mean dose 18.2 mg/day	OLA initiated at 15 mg/day, then 5–20 mg/day (191); mean dose 15.8 mg/day	104	ASE and active control statistically separated from PL. Completers were eligible for 9- [19] and 40-week [20] extension studies
McIntyre et al. [21]	3	Manic or mixed episode, bipolar I disorder	488	Initiated at 20 mg/day, then 10 or 20 mg/day (185); mean dose 18.4 mg/day	OLA initiated at 15 mg/day, then 5–20 mg/day (205); mean dose 15.9 mg/day	98	ASE and the active control statistically separated from PL. Completers were eligible for 9- [19] and 40-week [20] extension studies
Szegedi et al. [22]	12	Manic or mixed episode, bipolar I disorder	326	10 or 20 mg/day plus open label lithium or valproate (159); mean dose 11.8 mg/day	None	167	Adjunctive ASE was statistically superior to adjunctive PL at the 3-week primary efficacy endpoint. Completers were eligible for a 40-week extension study [22]

[a] Outcomes based on the Brief Psychiatric Rating Scale and/or Positive and Negative Syndrome Scale for the schizophrenia studies or the Young Mania Rating Scale for the bipolar studies, unless otherwise noted

ASE asenapine, *HAL* haloperidol, *LOCF* last observation carried forward, *NSA* Negative Symptom Assessment, *OLA* olanzapine, *PL* placebo, *RIS* risperidone

Asenapine's efficacy in the prevention of relapse was tested in a maintenance study whereby patients with schizophrenia were stabilized on asenapine during a 26-week open-label treatment period and then randomized to either continue asenapine or to receive placebo, double-blind, for up to an additional 26 weeks [14]. Asenapine was flexibly dosed at 5 or 10 mg bid. Of the 700 enrolled patients who were treated with open-label asenapine, 386 met stability criteria and entered the double-blind phase. Times to relapse/impending relapse and to discontinuation for any reason were significantly longer with asenapine than with placebo. The incidence of relapse/impending relapse was 12 % for asenapine and 47 % for placebo, yielding an NNT of 3 (95 % CI 3–4). Completion rates were 70 % for asenapine and 37.5 % for placebo, yielding an NNT of 4 (95 % CI 3–5). Interestingly, the most commonly used dose of asenapine was 10 mg bid in both the open-label and the double-blind phases, even though in the acute pivotal trials it was the 5-mg bid dose, and not the 10-mg bid dose that demonstrated efficacy (see Table 5).

Several longer-term head-to-head randomized trials were conducted that compared asenapine and olanzapine in patients with schizophrenia. Negative symptoms were the focus of two identically designed 26-week studies and their respective 26-week extensions [17]. Asenapine was not superior to olanzapine in change in the 16-item Negative Symptom Assessment Scale total score in either core study, but asenapine was superior to olanzapine at week 52 in one of the extension studies. In the two core studies, 26-week completion rates with asenapine were 64.7 and 49.6 % versus 80.4 and 63.8 %, respectively, with olanzapine, yielding NNTs in favor of olanzapine of 7 (95 % CI 5–13) and 7 (95 % CI 5–19), respectively. In the two extension studies, completion rates were 84.3 and 66.3 % with asenapine versus 89.0 and 80.9 %, respectively, with olanzapine, yielding NNTs in favor of olanzapine of 22 (ns) and 7 (95 % CI 4–45), respectively.

In another comparison of asenapine with olanzapine, patients with schizophrenia or schizoaffective disorder were randomly assigned to receive asenapine (flexibly dosed at 5 or 10 mg bid) or olanzapine (flexibly dosed at 10 or 20 mg/day) for up to 1 year [15], with completers eligible to participate in an extension study [16]. Rates of discontinuation because of insufficient therapeutic effect were 25.1 % for asenapine and 14.5 % for olanzapine, yielding an NNT advantage for olanzapine of 10 (95 % CI 7–18). Changes from baseline in PANSS total score were similar for asenapine and olanzapine at week 6 but showed a statistically significant difference in favor of olanzapine at endpoint (last observation carried forward), but among completers, changes in PANSS total scores were similar for asenapine versus olanzapine at week 6 and at week 52.

Efficacy for asenapine in the treatment of manic or mixed episodes of bipolar I disorder is supported by several trials, including the two 3-week phase III randomized, placebo- and olanzapine-controlled trials [18, 21], their common extension trials [19, 20], and a placebo-controlled adjunctive therapy trial with either lithium or valproate [22], and its extension [22]. For each study, YMRS total scores were statistically significantly improved from baseline to endpoint for asenapine and olanzapine (where applicable) compared with placebo. Percentages of subjects meeting criteria for response (≥50 % decrease from baseline YMRS total score) and remission (YMRS total score ≤12) were reported. In the monotherapy trials, responder rates were 43, 34, and 55 % for asenapine, placebo, and olanzapine, respectively, in one study [21], and 42, 25, and 50 %, respectively, in the other study [18]. This yielded for asenapine NNTs for response versus placebo of 12 (ns) and 6 (95 % CI 3–17) for each study, respectively; for olanzapine the respective NNT values were 5 (95 % CI 3–12) and 5 (95 % CI 2–8). The remission rates were 36, 31, and 46 % for asenapine, placebo, and olanzapine, respectively, in one study, and 40, 22, and 39 %, respectively, in the other study. This yielded for asenapine NNTs for remission versus placebo of 22 (ns) and 6 (95 % CI 3–14) for each study, respectively; for olanzapine, the respective NNT values were 7 (95 % CI 3–26) and 6 (95 % CI 3–16). In the adjunctive asenapine trial, responder rates for adjunctive asenapine versus adjunctive placebo were 34 versus 27 % at 3 weeks and 48 versus 34 % at 12 weeks, yielding NNT values of 14 (ns) at 3 weeks and 8 (95 % CI 5–38) at 12 weeks. In that same trial, remission rates for adjunctive asenapine versus adjunctive placebo were 34 versus 22 % at 3 weeks and 43 versus 30 % at 12 weeks, yielding NNT values of 9 (95 % CI 5–43) at 3 weeks and 8 (95 % CI 5–38) at 12 weeks. In the 9-week extension study for the monotherapy asenapine studies, the primary efficacy analysis demonstrated that asenapine was statistically non-inferior to olanzapine as measured by the YMRS total score from baseline to day 84 for the observed case subjects who had 3 weeks of previous exposure to study medication [19]. YMRS responder and remitter rates were similar for the asenapine and olanzapine groups: the rates of response at last observation carried forward endpoint were 77 and 82 % with asenapine and olanzapine, respectively, and the rates of remission were 75 and 79 %, respectively. In subjects subsequently enrolled in the 40-week extension study [20], maintenance of efficacy was observed for both asenapine and olanzapine, with no differences in response or remission rates.

5.2.3 Tolerability and Safety

Commonly observed adverse reactions in short-term trials (incidence ≥5 % and twofold greater than placebo) were akathisia, oral hypoesthesia, and somnolence for patients with schizophrenia; somnolence, dizziness, extrapyramidal symptoms other than akathisia, and increased weight for patients with bipolar disorder (monotherapy); and somnolence and oral hypoesthesia for patients with bipolar disorder (adjunctive) [54]. The rates and NNH versus placebo for these are summarized in Table 6. With the exception of three fixed-dose trials in schizophrenia, data are from flexible-dose studies. In addition, for the bipolar monotherapy trials, the starting dose was 10 mg bid, with a fallback to 5 mg bid if needed. For the adjunctive asenapine bipolar trial, the starting dose was 5 mg bid, with a possible increase to 10 mg bid if needed. Regardless of dose, somnolence is the single most common adverse event associated with asenapine treatment. The product label describes somnolence as usually transient, with the highest incidence reported during the first week of treatment [54]. The highest rates were observed in the short-term acute mania/mixed bipolar trials, where somnolence was reported in 24 % of patients receiving asenapine compared with 6 % of placebo patients, resulting in an NNH of 6 (95 % CI 5–9). Although somnolence was frequently reported, somnolence/sedation led to discontinuation in only a small proportion (0.6 %) of patients treated with asenapine [54]. Even though dizziness, postural hypotension, and possibly syncope would be expected given asenapine's potent alpha 1 noradrenergic antagonist activity, the observed rates of syncope were low among patients (0.17 % for patients receiving asenapine in the acute schizophrenia trials versus 0.26 % for placebo; 0.3 % of patients receiving asenapine in the acute bipolar monotherapy trials versus 0 for placebo) in contrast to that observed among healthy volunteers in the clinical pharmacology trials [51]. Asenapine 10 mg bid appears to be associated with a greater liability for akathisia than the 5 mg bid regimen [54]. Somewhat unique to asenapine is the possibility of oral hypoesthesia (numbness) or dysgeusia (distorted, altered, or unpleasant taste). Although rates of spontaneously reported oral hypoesthesia and dysgeusia were very modest in the clinical trials, patients in clinical practice may more readily complain about these potential effects and should be forewarned in order to avoid non-adherence. The black cherry-flavored formulation may lessen unpleasant taste.

The mean weight gain observed in the acute schizophrenia trials was 1.1 kg for asenapine versus 0.1 kg for placebo [54]. Among these patients, the proportion with a ≥7 % increase in body weight (at endpoint) was 4.9 % for asenapine versus 2 % for placebo [54], yielding an NNH versus placebo of 35 (95 % CI 20–132) [51]. In the acute bipolar monotherapy trials, the mean weight gain for asenapine was 1.3 kg versus 0.2 kg for placebo [54]. Among these patients, the proportion with a ≥7 % increase in body weight (at endpoint) was 5.8 % for asenapine versus 0.5 % for placebo [54], for an NNH of 19 (95 % CI 13–37) [51]. In the 52-week

Table 6 Asenapine: incidence and number needed to harm (95 % CI) versus placebo for treatment-emergent adverse events as reported in product labeling for events with incidence ≥5 % and twofold greater than placebo in acute studies (adapted with permission from Citrome [51])

Adverse event	Placebo	Asenapine 5 or 10 mg BID		Asenapine 5 mg BID		Asenapine 10 mg BID	
	Incidence (%)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)
Schizophrenia	$N = 378$	$N = 572$		$N = 274$		$N = 208$	
Somnolence	7	13	17 (11–43)	15	13 (8–32)	13	18 (10–221)
Akathisia	3	6	34 (18–249)	4	100 (ns)	11	13 (8–30)
Oral hypoesthesia	1	5	25 (17–52)	6	20 (13–50)	7	17 (11–42)
Bipolar disorder (monotherapy)	$N = 203$	$N = 379$					
Somnolence	6	24	6 (5–9)				
Dizziness	3	11	13 (9–25)				
Extrapyramidal symptoms other than akathisia	2	7	20 (13–56)				
Weight increased	<1	5	25 (16–71)				
Bipolar disorder (adjunctive)	$N = 166$	$N = 158$					
Somnolence	10	22	9 (5–25)				
Oral hypoesthesia	0	5	20 (12–63)				

BID twice daily, *CI* confidence interval, *NNH* number needed to harm

ns not statistically significant (the 95 % CI encompasses infinity)

study comparing asenapine with olanzapine in patients with schizophrenia or schizoaffective disorder [15], the mean weight gain from baseline observed with asenapine was 0.9 kg (at endpoint) and 1.6 kg (observed cases), compared with 4.2 kg (at endpoint) and 5.6 kg (observed cases) for olanzapine; the proportion of patients with a ≥7 % increase in body weight for asenapine was 14.7 % (at endpoint) and 22.5 % (observed cases). For olanzapine-treated patients in that study, the proportion of patients with a ≥7 % increase in body weight was 36.1 % (at endpoint) and 44.4 % (observed cases), yielding an NNH for olanzapine versus asenapine of 5 (95 % CI 4–7) for both the endpoint and observed cases analyses [51]. Overall, asenapine treatment had no significant effect on clinical laboratory parameters [54]. Table 7 summarizes the proportions of patients in the acute studies with abnormal metabolic variables at endpoint as noted in product labeling [54]; NNH values for asenapine versus placebo appear relatively benign. Long-term data regarding metabolic outcomes extending out to 12 months and beyond are consistent with the short-term data [15, 16, 54].

Asenapine has a mild effect on the ECG QTc interval similar to that seen with quetiapine, as evidenced in a dedicated QT study with doses of asenapine as high as 40 mg/day [68]. Asenapine was associated with increases in QTc interval ranging from 2 to 5 ms compared with placebo; no patients treated with asenapine experienced QTc increases ≥60 ms from baseline measurements, nor did any patient experience a QTc of ≥500 ms [54].

The effects on prolactin levels in the short-term schizophrenia and bipolar mania/mixed studies revealed no clinically relevant changes. Data are available from all subjects in the phase II and III clinical program for asenapine doses of 5–10 bid for shifts to higher than normal levels of prolactin, and these shifts were observed in 19, 44, 97, 72, and 51 % of subjects randomized to placebo, asenapine, risperidone, haloperidol, and olanzapine, respectively; yielding NNH versus placebo values of 4 (95 % CI 4–5), 2 (95 % CI 2–2), 2 (95 % CI 2–3), and 4 (95 % CI 3–4) for asenapine, risperidone, haloperidol, and olanzapine, respectively [51]. In the acute schizophrenia trials, mean decreases in prolactin levels were observed: 6.5 ng/mL for asenapine versus 10.7 ng/mL for placebo [54]; the proportion of patients with prolactin elevations ≥ 4 times the upper limit of normal were 2.6 % for asenapine versus 0.6 % for placebo [54], for an NNH of 50 (95 % CI 29–208) [51]. In the acute bipolar monotherapy trials, a mean increase in prolactin level of 4.9 ng/mL was observed for asenapine versus a decrease of 0.2 ng/mL for placebo [54]; the proportion of patients with prolactin elevations ≥4 times the upper limit of normal were 2.3 % for asenapine versus 0.7 % for placebo, for an NNH of 63 (ns) [54]. In the long-term trial of asenapine and olanzapine in schizophrenia and schizoaffective disorder, plasma prolactin levels decreased from elevated levels at baseline in both treatment groups [15].

5.2.4 Summary of Clinical Utility

NNT for efficacy for asenapine versus placebo for acute schizophrenia, using a threshold of a ≥30 % reduction from baseline on the total PANSS score, ranged from 5 (95 % CI 3–11) for 5 mg bid in one study [13] to 8 (ns) in

Table 7 Asenapine: incidence of subjects with abnormal values for metabolic variables at endpoint and number needed to harm (95 % CI) versus placebo

Metabolic variable	Placebo	Asenapine (any dose)	
	Incidence (%)	Incidence (%)	NNH (95 % CI)
Schizophrenia			
Fasting serum glucose ≥126 mg/dL at endpoint	6	7.4	72 (ns)
Total cholesterol ≥240 mg/dL at endpoint	7	8.3	77 (ns)
Triglycerides ≥200 mg/dL at endpoint	10.5	13.2	38 (ns)
Bipolar disorder (monotherapy)			
Fasting serum glucose ≥126 mg/dL at endpoint	2.2	4.9	38 (ns)
Total cholesterol ≥240 mg/dL at endpoint	8.6	8.7	1,000 (ns)
Triglycerides ≥200 mg/dL at endpoint	11.4	15.2	27 (ns)

Data from the product label [54]; the product label did not contain the numerators and denominators necessary for the calculation of the 95 % CI but a prior review [51] noted they were all ns

CI confidence interval, *NNH* number needed to harm

ns not statistically significant (the 95 % CI encompasses infinity)

the other positive study [12]. When calculating the LHH and contrasting an NNT of 5 for efficacy with the NNH for adverse outcomes across the therapeutic dose range, LHH was 2.6–20 for akathisia (clear dose relationship), 7 for weight gain ≥7 % within 6 weeks, and 2.6–3.6 for somnolence.

NNT for response for asenapine versus placebo for acute bipolar mania/mixed episodes, as defined by a ≥50 % reduction from baseline on the total YMRS score, ranged from 6 (95 % CI 3–17) in one study [18] to 12 (ns) in the other positive study [21]. When calculating the LHH and contrasting an NNT of 6 for efficacy with the NNH for adverse outcomes (mostly at the dose of 10 mg bid), LHH was 3.3 for extrapyramidal symptoms other than akathisia, 3.2 for weight gain ≥7 % within 3 weeks, and 1.0 for somnolence. The NNT for response for adjunctive asenapine (mostly 5 mg bid) in bipolar mania/mixed episodes versus lithium or valproate monotherapy [22] was 9 (95 % CI 5–43) at 3 weeks and 8 (95 % CI 5–38) at 12 weeks; this also yields an LHH for response versus somnolence of 1.0. An LHH of 1.0 may be of concern in patients who are sensitive to somnolence.

Patients started on asenapine for the first time need to be informed that the medication differs from others that may have been prescribed for them in the past because asenapine is absorbed in the mouth, and will not work if swallowed; thus the recommendation that food or liquids be avoided for 10 min post-administration. Dysgeusia and hypoesthesia should be proactively mentioned so that patients are not surprised and adherence can be maintained. Overall, asenapine appears to have a relatively benign weight and metabolic profile, with a desirable NNH versus placebo for weight gain. No initial dose titration is required, potentially simplifying treatment.

5.3 Lurasidone

5.3.1 Pharmacodynamics and Pharmacokinetics

Lurasidone is a full antagonist at dopamine D2 and serotonin 5-HT2A receptors, with binding affinities (K_i) of 0.47 nM and 0.994 nM, respectively (see Table 1). However, lurasidone also has high affinity for serotonin 5-HT7 receptors (0.495 nM; comparable to dopamine D2 and 5-HT2A receptors) and is a partial agonist at 5-HT1A receptors with a K_i of 6.38 nM. This may be of potential interest because of pre-clinical findings of a possible pro-cognitive effect mediated by action at the serotonin 5-HT7 receptor [67]. The 5-HT1A receptor has been hypothesized as being potentially useful target for the treatment of major depressive disorder [69] and schizophrenia [70]. Low affinity to muscarinic receptors would theoretically predict a low propensity for causing anticholinergic side effects, including cognitive dysfunction and gastrointestinal disturbances, at clinically relevant doses [58]. Low affinity to histamine H1 receptors would theoretically predict a low propensity for causing sedation or weight gain [58].

In contrast to iloperidone and asenapine, lurasidone was tested in clinical trials where the medication was administered once rather than twice daily. However, food can affect the absorption of lurasidone, similar to what is observed with ziprasidone [71]. The caloric threshold (350 calories) is lower than that required with ziprasidone (500 calories). In the clinical trials, lurasidone was administered with a meal or within 30 min after eating [72]. In a food-effect study, lurasidone mean maximum plasma concentration and plasma exposure as measured by area under the curve were approximately three-times and two-times higher, respectively, when lurasidone was administered with food compared with the levels observed under fasting conditions [55]. Lurasidone exposure was not affected as the meal size was increased from 350 to 1,000 calories and was independent of the fat content of the meal [55]. Although the pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 20–160 mg [55], it has not been established that the same would hold true under fasting conditions.

Of clinical relevance is lurasidone's route of metabolism through cytochrome P450 (CYP)3A4 [55]. Lurasidone use is contraindicated in the presence of strong inducers and

inhibitors of CYP3A4 (such as rifampin and ketoconazole, respectively) because plasma levels of lurasidone would either be very low or very high, respectively. In the presence of moderate inhibitors of CYP3A4, the recommended starting dose of lurasidone is 20 mg/day, and the highest recommended dose under these circumstances is 80 mg/day.

5.3.2 *Efficacy*

When lurasidone was initially approved in the USA in 2010, the data available were limited to doses ranging from 20 to 120 mg/day studied in five similarly designed 6-week placebo-controlled studies, of which four were informative regarding efficacy [23–26] and one categorized as failed because neither lurasidone nor the active control (haloperidol) statistically separated from placebo on the primary outcome measure [48, 72] (see Table 8). Consequently, initial approval was limited to doses of 40 and 80 mg/day, with the 120 mg/day dose, although efficacious, not being approved because of an apparent increase in adverse effects at 120 mg/day [48, 72]. Once lurasidone was approved in the USA, additional data became available from another 6-week pivotal study that established lurasidone 160 mg/day as being efficacious and well tolerated [29], leading to a revision in product labeling [55] and recommending a new dose range of 40–160 mg/day. No initial dose titration is necessary, and clinicians are free to start at any dose, with the expectation that doses between 40 and 160 mg/day are therapeutic. A recommended time of administration is not provided in product labeling; however, in earlier studies, lurasidone was administered in the morning and in later studies, including the study where 160 mg/day was found efficacious and well tolerated, lurasidone was administered in the evening.

Efficacy outcomes of lurasidone appeared similar to those observed for olanzapine and quetiapine extended release in the acute studies where these agents served as active controls [26, 29]. Lurasidone appeared to have similar efficacy to ziprasidone as evidenced in a 3-week non-placebo-controlled study [31, 32]. A 6-week placebo-controlled and risperidone-controlled study conducted in Japan, Korea, and Taiwan, failed to evidence efficacy for either lurasidone or risperidone when compared with placebo [40, 73].

NNTs for categorical response from the five short-term clinical trials that were considered supportive for drug approval [23–26, 29] are available in a published report [40]. Data were pooled and responder rates as defined by a reduction of ≥20, 30, 40, or 50 % from baseline on the PANSS total score were used to determine NNT versus placebo. For PANSS reductions ≥30 %, NNTs were 6 (95 % CI 5–10), 6 (95 % CI 5–10), 7 (95 % CI 5–12), and 4 (95 % CI 3–5) for lurasidone doses of 40, 80, 120, and 160 mg/d, respectively, and 4 (95 % CI 3–5) and 3 (95 % CI 3–4) for olanzapine 15 mg/d and quetiapine extended release 600 mg/d, respectively.

Long-term data are also available, and randomized double-blind trials include comparisons with risperidone in a 12-month safety study [30], and quetiapine extended release in a recently published 12-month double-blinded extension to one of the short-term pivotal trials [74]. In the lurasidone versus risperidone study, comparable improvements in efficacy measures were observed with both agents and the rates of relapse were similar; however, all-cause discontinuation rates were higher for lurasidone versus risperidone, with an NNT advantage for risperidone of 9 (95 % CI 5–26) [30]. In the lurasidone versus quetiapine extended release study, subjects received flexible once-daily doses of lurasidone (40–160 mg) or quetiapine extended release (200–800 mg) [74]. Lurasidone was non-inferior to quetiapine in risk for relapse over the 12-month treatment period. The risk of relapse in lurasidone-treated subjects was reduced by 27.2 % (hazard ratio 0.728) compared with quetiapine and the Kaplan–Meier estimate of the probability of relapse at 12 months was lower for lurasidone than for quetiapine (0.237 versus 0.336), with an NNT advantage for lurasidone of 11 (ns). Treatment with lurasidone (modal daily dose 120 mg) was associated with a significantly greater change in PANSS total scores than treatment with quetiapine (modal dose 600 mg). A more traditional relapse-prevention study of lurasidone versus placebo is underway (NCT01435928).

5.3.3 *Tolerability and Safety*

Commonly observed adverse reactions in short-term trials in patients with schizophrenia (incidence ≥5 % and two-fold greater than placebo) were somnolence, akathisia, nausea, and parkinsonism [55]. The rates and NNH versus placebo for these are summarized in Table 9. When lurasidone was initially approved, it was believed that doses above 80 mg/day did not appear to confer added benefit but may be associated with a dose-related increase in somnolence and akathisia. With the availability of results from a study that contrasted lurasidone 80 and 160 mg/day versus placebo [29], this dose relationship for adverse events was not evidenced for lurasidone 160 mg/day. As noted earlier, the short-term pivotal trials were similarly designed except that the earlier trials dosed lurasidone in the mornings and the newer trials, including the study that tested lurasidone 160 mg/day, dosed lurasidone in the evening. When pooling all doses of lurasidone from the short-term clinical trials (20–160 mg/day), somnolence and akathisia share almost the same NNH versus placebo −11 and 10, respectively (respective 95 % CIs 8–14 and 9–13); nausea

Table 8 Completed lurasidone double-blind randomized controlled trials for which results are available

Study	Duration (weeks)	Disease state	N Randomized	LUR dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
Ogasa et al. [23]	6	Acute schizophrenia	149	40 mg/day (50), 120 mg/day (49)	None	50	LUR 40 and 120 mg/day were each statistically significantly superior to PL
See review [48, 72]	6	Acute schizophrenia	356	20 mg/day (71), 40 mg/day (69), 80 mg/day (71)	HAL 10 mg/day (73)	72	LUR 20, 40, or 80 mg/day and active control did not separate statistically from PL. Study conducted in USA
Nakamura et al. [24]	6	Acute schizophrenia	180	80 mg/day (90)	None	90	LUR statistically significantly superior to PL
Nasrallah et al. [25]	6	Acute schizophrenia	500	40 mg/day (125), 80 mg/day (123), 120 mg/day (124)	None	128	LUR 80, but not 40 or 120 mg/day, was statistically significantly superior to PL. Completers eligible to enter a 22-month extension study. Observed-case analysis ($N = 250$) was presented in a poster [75]
Meltzer et al. [26]	6	Acute schizophrenia	478	40 mg/day (120), 120 mg/day (119)	OLA 15 mg/day (123)	116	LUR 40, 120 mg/day and active control were statistically significantly superior to PL. Completers ($N = 298$) eligible to enter 6-month extension study; 254 did so [27]
Loebel et al. [29]	6	Acute schizophrenia	488	80 mg/day (125), 160 mg/day (121)	QXR 600 mg/day (120)	122	LUR 80, 160 mg/day and active control were statistically significantly superior to PL. Completers ($N = 353$) eligible to enter 1-year extension study; 236 did so [74]
Loebel et al. [74]	1 year	Schizophrenia	292	40–160 mg/day (151 + 56)	QXR 200–800 mg/day (85)	None	Double-blind extension to [29]. LUR met noninferiority criteria versus QXR, and was associated with higher rates of remission, and reduced risk of hospitalization. An additional 56 pts receiving PL in [29] received LUR in the extension and were included in secondary efficacy and safety analyses
NCT00711269 [72, 73]	6	Schizophrenia	447	40 mg/day (125), 80 mg/day (129)	RIS 4 mg/day (64)	129	Neither LUR 40, 80 mg/day nor active control separated statistically from PL. Study conducted in Japan, Korea, Taiwan
Potkin et al. [31]	3	Schizophrenia or schizoaffective disorder; non-acute	301	120 mg/day (150)	ZIP 80 mg BID (151)	None	Proportion of pts who discontinued from study was similar for LUR and ZIP. Reductions in psychopathological rating scale scores were also similar. Cognitive change described in a separate report [32]

Table 8 continued

Study	Duration (weeks)	Disease state	N Randomized	LUR dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
Citrome et al. [30]	1 year	Schizophrenia or schizoaffective disorder; non-acute	629	40–120 mg/day (427); mean dose 85 mg/day	RIS 2–6 mg/day (202); mean dose 4.3 mg/day	None	Comparable improvement in efficacy measures observed with both LUR and RIS; relapse rates were similar. All-cause discontinuation rates were higher for LUR versus RIS
Loebel et al. [76]	6	Bipolar I depression	505	20–60 mg/day (166) (mean dose 35 mg/day), 80–120 mg/day (169) (mean dose 91 mg/day)	None	170	LUR significantly reduced depressive symptoms versus PL
Loebel et al. [77]	6	Bipolar I depression	348	20–120 mg/day (183); mean dose 66 mg/day	None	165	Adjunctive LUR significantly reduced depressive symptoms versus adjunctive PL

[a] Outcomes based on the Brief Psychiatric Rating Scale and/or Positive and Negative Syndrome Scale for the schizophrenia studies or the Montgomery–Asberg Depression Rating Scale for the bipolar depression studies, unless otherwise noted

BID twice daily, *HAL* haloperidol, *LUR* lurasidone, *OLA* olanzapine, *PL* placebo, *pts* patients, *QXR* quetiapine extended-release, *RIS* risperidone, *ZIP* ziprasidone

and parkinsonism both have an NNH versus placebo of 20 (95 % CI for both 14–36). When evaluating the 160 mg/day dose versus placebo in an analysis of pooled data, the NNH for akathisia was 22 (ns), somnolence 36 (ns), nausea 82 (ns), and parkinsonism 20 (95 % CI 11–198) [40].

The mean weight gain observed in the acute schizophrenia trials was 0.43 kg for lurasidone versus –0.02 kg for placebo; in contrast, change in weight from baseline for olanzapine was 4.15 kg and for quetiapine extended release was 2.09 kg in the studies where these agents served as active controls [55]. The proportion of patients with a ≥7 % increase in body weight (at endpoint) was 4.8 % for lurasidone and 3.3 % for placebo [55], for an NNH of 67 (ns); in contrast, the corresponding NNH versus placebo for olanzapine was 4 (95 % CI 3–5) and for quetiapine extended release was 9 (95 % CI 6–22) in the studies where these agents served as active controls [40]. As per product labeling, in the uncontrolled, longer-term studies (primarily open-label extension studies), lurasidone was associated with a mean change in weight of −0.69 kg at week 24, −0.59 kg at week 36, and −0.73 kg at week 52. Table 10 summarizes the proportions of patients in the acute studies with shifts to abnormal in values for metabolic variables [55]; NNH values for lurasidone versus placebo appear relatively benign. Long-term data regarding metabolic outcomes extending out to 12 months are consistent with the short-term data [55]. In addition to the data in product labeling, the metabolic profile of lurasidone appears similar to that for ziprasidone based on a 3-week study [31]. In the 12-month safety study of lurasidone versus risperidone [30], a higher proportion of patients receiving risperidone had a ≥7 % endpoint increase in weight (14 versus 7 %, for an NNH disadvantage for risperidone of 16 [95 % CI 9–104]); the median endpoint change in prolactin was significantly higher for risperidone and the proportion of shifts from low/normal prolactin to high prolactin levels in men were 13 versus 35 %, for lurasidone and risperidone, respectively, and 12 versus 50 % for women, respectively, yielding NNH disadvantages for risperidone of 5 (95 % CI 4–8) for men and 3 (95 % CI 2–4) for women. In the lurasidone clinical trial program, dose-related prolactin elevation was noted with greater effects in women than in men [55]. However, in most cases, these effects may not be clinically relevant as the proportion of patients with prolactin elevations ≥5 times the upper limit of normal was 2.8 % for lurasidone versus 1.0 % for placebo, yielding an NNH of 56 (95 % CI 35–151), and in the uncontrolled longer-term studies, lurasidone was associated with a median change in prolactin of −0.9 ng/mL at week 24, −5.3 ng/mL at week 36 and −2.2 ng/mL at week 52 [55].

Lurasidone does not appear to impact on the ECG QT interval. In a dedicated QT study, the effects of lurasidone 120 and 600 mg/day on the QTc interval were evaluated and there was no apparent dose (exposure)-response relationship [55]. In short-term, placebo-controlled studies, no post-baseline QT prolongations exceeding 500 ms were reported in patients treated with lurasidone or placebo.

Table 9 Lurasidone: incidence and number needed to harm (95 % CI) versus placebo for treatment-emergent adverse events as reported in product labeling for events with incidence ≥5 % and twofold greater than placebo in acute studies of schizophrenia (adapted/updated with permission from Citrome [48])

Adverse event	Placebo ($N = 708$)	Lurasidone 20–160 mg/day ($N = 1,508$)	
	Incidence (%)	Incidence (%)	NNH (95 % CI)
Akathisia	3	13	10 (9–13)
Somnolence	7.1	17.0	11 (8–14)
Nausea	5	10	20 (14–36)
Parkinsonism	5	10	20 (14–36)

CI confidence interval, *NNH* number needed to harm

ns not statistically significant (the 95 % CI encompasses infinity)

Additional safety information is available from reports of study extensions to several of the 6-week pivotal trials. In the 6-month, open-label extension for the 6-week study that included olanzapine as an active control, patients received flexible doses of lurasidone in the range of 40–120 mg/day [27]. Two AEs occurred with an incidence >10 %: akathisia (13.0 %) and insomnia (11.0 %). Body weight remained relatively stable during the open-label extension, except for patients who had been randomized in the initial double-blind phase to olanzapine 15 mg/day, where a mean reduction of −1.8 kg in weight was observed after the switch to open-label lurasidone. In the 12-month, double-blind extension for the 6-week study that included quetiapine extended release as an active control, patients received flexible daily doses of lurasidone in the range of 40–160 mg or quetiapine extended release 200–800 mg; rates of adverse events ≥5 % in the lurasidone group were akathisia (12.6 %), headache (10.6 %), insomnia (7.9 %), anxiety (6.0 %), parkinsonism (6.0 %), and weight increase (6.0 %). Observed case analysis of lurasidone versus quetiapine showed a mean change in weight of +0.7 versus +1.2 kg; a median change in glucose of +1.0 versus +1.0 mg/dL; a median change in cholesterol of 0.0 versus +4.0 mg/dL; and a median change in triglycerides of −18.0 versus −7.0 mg/dL [74]. In the 22-month, open-label extension for a 6-week study that tested lurasidone 40, 80, and 120 mg/day, patients received flexible doses of lurasidone in the range of 40–120 mg/day [76]. Three adverse events occurred in ≥10 % of subjects: schizophrenia (12.4 %), akathisia (10.8 %), and somnolence (10.8 %); and 19.2 % reported at least one movement disorder-related adverse event. Minimal effects on weight, glucose, and lipids were observed.

The results of a 6-week switch study have been recently published [28]. In this trial, the safety, tolerability, and

Table 10 Lurasidone: incidence of shifts to abnormal range for metabolic variables (fasting) and number needed to harm (95 % CI) versus placebo in acute studies of schizophrenia

Metabolic variable	PL	LUR 20 mg/day		LUR 40 mg/day		LUR 80 mg/day		LUR 120 mg/day		LUR 160 mg/day	
	Incidence (%)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)
Serum glucose shifts to ≥126 mg/dL	52/628 (8.3)	7/60 (11.7)	30 (ns)	57/449 (12.7)	23 (13–153)	32/472 (6.8)	−67 (ns)	26/260 (10.0)	59 (ns)	6/108 (5.6)	−37 (ns)
Total cholesterol shifts to ≥240 mg/dL	30/571 (5.3)	8/58 (13.8)	12 (ns)	25/402 (6.2)	104 (ns)	23/434 (5.3)	2,193 (ns)	9/238 (3.8)	−68 (ns)	4/101 (4.0)	−78 (ns)
Triglycerides shifts to ≥200 mg/dL	53/526 (10.1)	7/49 (14.3)	24 (ns)	41/379 (10.8)	135 (ns)	25/400 (6.3)	−27 (−14 to − 306)	22/209 (10.5)	223 (ns)	7/100 (7.0)	−33 (ns)

Data from the product label [55]

CI confidence interval, *LUR* lurasidone, *NNH* number needed to harm, *PL* placebo

ns not statistically significant (the 95 % CI encompasses infinity)

effectiveness of switching clinically stable, but symptomatic, non-acute patients with schizophrenia or schizoaffective disorder to lurasidone was assessed. A total of 240 subjects were randomized to three switch strategies involving different starting doses of lurasidone ranging from 40 to 80 mg/day, while the prior antipsychotic agent was tapered and discontinued over the initial 2-week study period. Switching to lurasidone was well tolerated, with 81 % of entered patients completing the 6-week study. No clinically relevant differences in efficacy or tolerability were noted when comparing the three different switch strategies. Patients switching to lurasidone demonstrated clinically relevant improvement in efficacy measures. Overall reductions in weight, lipids, and glucose were observed, and the adverse event profile was similar to that of previous lurasidone studies.

5.3.4 Bipolar I Depression

Data as presented in posters are available from two 6-week, placebo-controlled trials in major depressive episodes in patients with bipolar I disorder (with or without rapid cycling and without psychotic features): a monotherapy study [76], and an adjunctive therapy trial [77]. The FDA approved lurasidone for this indication on 28 June 2013 [78].

See Table 8. Responder rates (response defined as a ≥50 % reduction in the Montgomery–Asberg Depression Rating Scale (MADRS) total score at endpoint) were 53 % for lurasidone 20–60 mg/day, 51 % for lurasidone 80–120 mg/day, and 30 % for placebo, for an NNT versus placebo of 5 (95 % CI 3–8) and 5 (95 % CI 4–11) for lurasidone 20–60 mg/day and 80–120 mg/day, respectively. Remission rates (remission defined as a MADRS total score ≤12 at endpoint) were 42 % for lurasidone 20–60 mg/day, 40 % for lurasidone 80–120 mg/day, and 25 % for placebo, for an NNT versus placebo of 6 (95 % CI 4–14) and 7 (95 % CI 4–21) for lurasidone 20–60 mg/day and 80–120 mg/day, respectively. In the adjunctive therapy trial [77], responder rates were 57 % for lurasidone and 42 % for placebo, for an NNT versus placebo of 7 (95 % CI 4–24). Remission rates were 50 % for lurasidone and 35 % for placebo, for an NNT versus placebo of 7 (95 % CI 4–23). For both the monotherapy and the adjunctive lurasidone studies, the tolerability and safety outcomes were consistent with those observed in the trials in patients with schizophrenia.

5.3.5 Summary of Clinical Utility

NNT for efficacy for lurasidone versus placebo for acute schizophrenia, using a threshold of a ≥30 % reduction from baseline on the total PANSS score, ranged from 4 (95 % CI 3–5) for 160 mg/day to 7 (95 % CI 5–12) for 120 mg/day [40]. Pooling all doses from 40 to 160 mg/day, NNT is 6 (95 % CI 5–8). When calculating the LHH and contrasting an NNT of 6 for efficacy with the NNH for adverse outcomes across the therapeutic dose range, LHH was 1.7 for akathisia, 11.2 for weight gain ≥7 % within 6 weeks, and 1.7 for somnolence. LHH for the treatment of bipolar depression would be similar.

Lurasidone is associated with minimal weight gain (appears best in class) and no clinically meaningful alterations in glucose, lipids, prolactin, or the ECG QT interval. Lurasidone differs from iloperidone and asenapine in terms of the recommended dosing frequency (once daily versus bid); however, lurasidone must be administered with a meal. No initial dose titration is required, potentially simplifying treatment.

5.4 Cariprazine

5.4.1 Pharmacodynamics and Pharmacokinetics

Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist presently under consideration by the FDA for the treatment of schizophrenia and bipolar disorder [36–38]. See Table 1. Binding affinities (K_i) for dopamine D3 receptors (0.085) are an order of magnitude higher than for D2 receptors (0.49–0.69). At present, the only dopamine D2 partial agonist commercially available for the treatment of psychiatric disorders is aripiprazole [79]. Cariprazine is also a partial agonist at serotonin 5-HT1A receptors with a K_i of 3. Differing from many other second-generation antipsychotics, cariprazine's binding at serotonin 5-HT2A receptors is relatively weaker, with a K_i of 19.

Theoretically, dopamine D3-preferring agents may exert pro-cognitive effects, as evidenced in animal studies [80]. Serotonin 5-HT1A partial agonism, a property cariprazine also shares with aripiprazole and lurasidone, is also thought to possibly benefit negative symptoms and cognitive deficits [69, 70].

In the clinical trials, cariprazine was titrated to target doses. There are two active metabolites of note: desmethyl-cariprazine and didesmethyl-cariprazine. The half-life of didesmethyl-cariprazine is substantially longer than that of cariprazine, and systemic exposure to didesmethyl-cariprazine can be several times higher than that for cariprazine [36–38].

5.4.2 Efficacy

Four phase II or III, 6-week, randomized controlled trials in acute schizophrenia have been completed and reported as poster presentations or in press releases by the manufacturer [81–84]. Three of the four studies can be considered positive. See Table 11. Superiority over placebo on the PANSS total score was evidenced for cariprazine in daily

Table 11 Completed cariprazine double-blind randomized controlled trials for which results are available

Study	Duration (weeks)	Phase and disease state	N Randomized	CAR dose (*N*)	Active control dose (*N*)	N PL	Comments regarding efficacy outcomes[a]
Litman et al. [81]	6	II; acute schizophrenia	392	1.5–4.5 mg/day (128), 6–12 mg/day (134)	None	130	For primary efficacy parameter, overall *P*-value comparing the three tx groups was not statistically significant. Pairwise comparison between each CAR dose group and PL yielded significant superiority for the low- but not high-dose group
Bose et al. [82]	6	II; acute schizophrenia	732	1.5 mg/day (145), 3.0 mg/day (147), 4.5 mg/day (148)	RIS 4.0 mg/day (141)	151	All doses of CAR and the active control were statistically superior to PL. A 48-week ol extension to this study was also completed ($N = 97$); data presented as a poster [88]
Zukin et al. [83]	6	III; acute schizophrenia	446	3–6 mg/day (151) (mean dose 4.2 mg/day), 6–9 mg/day (148) (mean dose 6.6 mg/day)	None	147	Both dose ranges of CAR were statistically superior to PL
Forest Laboratories [84]	6	III; acute schizophrenia	617	3 mg/day (ND), 6 mg/day (ND)	ARI 10 mg/day (ND)	ND	Both doses of CAR and active control were statistically superior to PL
Knesevich et al. [85]	3	II; manic or mixed episode, bipolar I disorder	238	3–12 mg/day (118); mean dose 8.8 mg/day	None	118	CAR was statistically superior to PL
Starace et al. [86]	3	III; manic or mixed episode, bipolar I disorder	312	3–12 mg/day (158); mean dose 7.5 mg/day	None	154	CAR was statistically superior to PL
Forest Laboratories [87]	3	III; manic or mixed episode, bipolar I disorder	497	3–6 mg/day (167), 6–12 mg/day (169)	None	161	Both dose ranges of CAR were statistically superior to PL
Forest Laboratories [89]	8	II; bipolar I or II depression without psychotic features	233	0.25–0.75 mg/day (ND), 1.5–3.0 mg/day (ND)	None	ND	CAR was not statistically superior to PL
Forest Laboratories [90]	8	II; major depressive disorder	231	0.1–0.3 mg/day (ND), 1–2 mg/day (ND)	None	ND	CAR was not statistically superior to PL

[a] Outcomes based on the Brief Psychiatric Rating Scale and/or Positive and Negative Syndrome Scale for the schizophrenia studies, the Young Mania Rating Scale for the bipolar mania studies, or the Montgomery-Asberg Depression Rating Scale for the depression studies

ARI aripiprazole, *CAR* cariprazine, *ND* not disclosed, *ol* open-label, *PL* placebo, *RIS* risperidone, *tx* treatment

doses of 1.5, 3.0, 4.5, 6.0, 1.5–4.5, 3.0–6.0, and 6.0–9.0 mg. Responder rates were provided for one of the studies [83], using a threshold of a ≥30 % improvement in the PANSS total score. Response was observed in 34.7, 28.6, and 24.8 % of subjects randomized to cariprazine 6–9, 3–6 mg/day, or placebo, respectively; this yields NNT versus placebo for response of 27 (ns) for cariprazine 3–6 mg/day and 11 (ns) for 6–9 mg/day.

Three phase II or III, 3-week, randomized controlled trials in bipolar mania or mixed episodes have been

Table 12 Cariprazine: incidence and number needed to harm (95 % CI) versus placebo for treatment-emergent adverse events for events with incidence ≥5 % and twofold greater than placebo in acute studies as reported in phase III studies, as available[a]

Adverse event	Placebo ($N = 147$)	Cariprazine 3–6 mg/day ($N = 151$)		Cariprazine 6–9 mg/day ($N = 148$)	
	Incidence (%)	Incidence (%)	NNH (95 % CI)	Incidence (%)	NNH (95 % CI)
Schizophrenia					
Akathisia	3	16	8 (6–16)	17	8 (5–14)
Restlessness	5	7	50 (ns)	10	20 (ns)
Extrapyramidal disorder	2	5	34 (ns)	10	13 (8–38)
Dyspepsia	3	2	NA	7	25 (ns)
Constipation	3	9	17 (9–150)	6	34 (ns)
Tremor	2	7	20 (11–292)	5	34 (ns)
Weight increased	1	3	50 (ns)	5	25 (13–726)
Diarrhea	1	5	25 (13–590)	4	34 (ns)

Adverse event	Placebo ($N = 154$)	Cariprazine 3–12 mg/day ($N = 158$)	
	Incidence (%)	Incidence (%)	NNH (95 % CI)
Bipolar disorder			
Akathisia	4.5	22.8	6 (4–10)
Extrapyramidal disorder	1.9	15.2	8 (6–14)
Tremor	3.9	11.4	14 (8–60)
Dyspepsia	3.2	10.8	14 (8–52)
Vomiting	3.9	10.1	17 (9–162)
Dizziness	3.9	8.2	24 (ns)
Diarrhea	1.3	7.0	18 (10–77)
Somnolence	1.3	5.7	23 (12–274)
Restlessness	0.6	5.7	20 (12–83)
Pyrexia	1.9	5.1	33 (ns)

[a] See Zukin et al. [83] and Starace et al. [86]

CI confidence interval, *NA* not applicable—rate lower for cariprazine than placebo, *NNH* number needed to harm, *ns* not statistically significant (the 95 % CI encompasses infinity)

completed and reported as poster presentations or in press releases by the manufacturer [85–87]. Superiority over placebo on the YMRS total score was evidenced for daily doses of cariprazine 3–12 mg/day. Response (≥50 % decrease from baseline YMRS total score) and remission rates (YMRS total score ≤12) are available for two of the trials [85, 86]. In the phase II trial [85], response rates were 48 % for cariprazine 3–12 mg/day and 25 % for placebo, for an NNT of 5 (95 % CI 3–10); remission rates were 42 versus 23 %, respectively, for an NNT of 6 (95 % CI 4–14). In the phase III trial [86], response rates were 59 % for cariprazine 3–12 mg/day and 44 % for placebo, for an NNT of 7 (95 % CI 4–25); remission rates were 52 versus 35 %, respectively, for an NNT of 6 (95 % CI 4–17).

Long-term efficacy data are not available. A traditional relapse-prevention study of cariprazine versus placebo is underway (NCT01412060).

5.4.3 Tolerability and Safety

Commonly observed adverse reactions (incidence ≥5 % and twofold greater than placebo) in the phase III short-term trials where data were available [83, 86] were akathisia, restlessness, extrapyramidal disorder, dyspepsia, constipation, tremor, weight increase, and diarrhea for patients with schizophrenia; and akathisia, extrapyramidal disorder, tremor, dyspepsia, vomiting, dizziness, diarrhea, somnolence, restless, and pyrexia for patients with bipolar disorder. The rates and NNH versus placebo for these are summarized in Table 12; these data must be considered preliminary; the availability of an integrated safety/tolerability summary as would be found in a product label is awaited. Separate tables for incidence of adverse events and NNH for the available phase II data can be found elsewhere [36, 37].

In the positive phase II acute schizophrenia study conducted with doses of cariprazine 1.5–4.5 mg/day [82], no clinically meaningful changes in metabolic variables, prolactin elevation, or QTc prolongation (>500 ms) were observed for cariprazine. Potentially clinically significant weight gain (≥7 % increase from baseline) was greater for risperidone (16.7 %) than cariprazine (8.5, 10.7, and 4.9 % for 1.5, 3.0, and 4.5 mg/day, respectively) or placebo (2 %), yielding an NNH versus placebo of 16 (95 % CI 9–69), 12 (95 % CI 8–31), 35 (ns), and 7 (95 % CI 5–13) for cariprazine 1.5, 3.0, and 4.5 mg/day, and risperidone subjects, respectively. Similarly, for the phase III acute schizophrenia study conducted with cariprazine doses 3–9 mg/day, and where results are available [83], no clinically meaningful changes in metabolic variables, prolactin elevation, or QTc prolongation (>500 ms) were observed for cariprazine. Mean change from baseline in body weight was 0.7, 0.9, and 1.2 kg in the placebo, cariprazine 3–6 mg/day, and 6–9 mg/day groups, respectively. Weight gain ≥7 % increase from baseline was observed for 8 % of patients receiving cariprazine 3–6 mg/day, 11 % for 6–9 mg/day, and 4 % for placebo, yielding an NNH versus placebo of 25 (ns), and 15 (95 % CI 8–96) for cariprazine 3–6 mg/day and 6–9 mg/day, respectively.

In the phase III acute mania study conducted with doses of cariprazine 3–12 mg/day (mean 7.5 mg/day) [86], no clinically meaningful changes in metabolic variables, prolactin elevation, or QTc prolongation (>500 ms) were observed for cariprazine. Mean changes from baseline to end of treatment in body weight were small and similar between treatment groups (placebo 0.30 kg; cariprazine 0.43 kg); categorical changes were not reported.

Results from a 48-week open-label extension study have also been presented [88]; treatment-emergent adverse events reported in ≥10 % of patients were akathisia, insomnia, and increased weight. Cariprazine 4.5 mg/day was the final dose for 70 % of the subjects and the modal dose for 68 %. Mean changes in clinical laboratory values were generally small. Mean prolactin levels decreased from baseline. No clinically significant trends or changes were noted on most metabolic variables, but insulin showed an increasing trend from baseline. Mean body weight increased by 1.87 kg from a lead-in baseline mean of 71.26 kg. Increase in weight of ≥7 % from baseline was observed in 33 % of subjects; decrease in weight by ≥7 % from baseline was observed in 8 % of subjects. Although mean and median changes in blood pressure and pulse rate parameters were small, orthostatic hypotension while changing from the supine to standing position were noted in 25 % of subjects. No signal was observed for abnormalities in the ECG QT interval. The rate of treatment-emergent parkinsonism (Simpson Angus Scale total score >3) was 8.6 % and was similar to the rate observed for cariprazine in the lead-in study (8.2–10.3 %) [82]. The rate of treatment-emergent akathisia (Barnes Akathisia Scale score >2) was 17.2 % and was higher than the rate observed in the lead-in study (11.0–15.1 %) [88]. There were no discontinuations because of treatment-emergent movement disorder-related adverse events.

5.4.4 Summary of Clinical Utility

Insufficient information is available regarding categorical efficacy outcomes for cariprazine in patients with schizophrenia to calculate an NNT with sufficient precision to then calculate LHH; however, the NNT versus placebo for response for the treatment of manic/mixed episodes of bipolar disorder was 5 (95 % CI 3–10) in the phase II trial [85] and 7 (95 % CI 4–25) in the phase III trial [86]. In subjects with schizophrenia in the available phase III study [83], the largest cariprazine–placebo differences in adverse event rates were observed for akathisia and extrapyramidal disorder, with corresponding NNH values of 8 (95 % CI 5–14) and 13 (95 % CI 8–38). This was also the case for subjects in the available bipolar mania/mixed episode phase III trial [86], with a resultant NNH versus placebo for akathisia of 6 (95 % CI 4–10) and for extrapyramidal disorder of 8 (95 % CI 6–14). Assuming an NNT of ~6 for response for the treatment of bipolar mania/mixed episodes, LHH was 1 for akathisia, 1.3 for extrapyramidal disorder, and 3.8 for somnolence. Categorical data for weight gain ≥7 % within 3 weeks for the bipolar mania/mixed episode trials are not available. NNH versus placebo for weight gain ≥7 % within 6 weeks in the acute schizophrenia trials ranged from 12 (95 % CI 8–31) to 35 (ns).

Although categorical data have not yet been presented regarding metabolic variables and prolactin levels, no clinically meaningful changes in metabolic variables or prolactin elevation have been evidenced in the clinical trials as reported. Moreover, cariprazine does not appear to be associated with effects on the ECG QT interval. If approved by regulatory authorities, cariprazine would join aripiprazole as the second dopamine receptor partial agonist antipsychotic available for clinical use. Cariprazine differs from aripiprazole in terms of dopamine D3 receptor selectivity. Further studies would be helpful to discern the distinguishing features of cariprazine from aripiprazole and other second-generation antipsychotics.

5.5 Brexpiprazole

5.5.1 Pharmacodynamics and Pharmacokinetics

Brexpiprazole is in phase III of clinical development for the treatment of schizophrenia and for adjunctive use in the

treatment of major depressive disorder. Limited information about brexpiprazole is available publicly. Brexpiprazole is a partial agonist at dopamine D2/D3 and serotonin 5-HT1A receptors and a potent antagonist of the serotonin 5-HT2A receptor, with K_i values of 0.3, 1.1, 0.12, and 0.47, respectively [91]. Brexpiprazole is also an antagonist at the noradrenergic alpha 1 receptor, with a K_i 3.8 and has relatively low affinity at histamine H1 and muscarinic M1 receptors [91]. Compared with aripiprazole, affinity at the dopamine D2 receptor for brexpiprazole is approximately three times higher, affinity at the serotonin 5-HT2A and 5-HT1A receptors approximately ten times higher, and affinity at the noradrenergic alpha 1 receptor somewhat more than ten times higher. The clinical relevance of these differences awaits the conduct of appropriately designed clinical trials.

5.5.2 *Efficacy*

The preliminary results of a 6-week double-blind, placebo- and aripiprazole-controlled phase II study that explored the dose-response relationship of brexpiprazole in acutely ill patients with schizophrenia have been presented [92]. A total of 459 patients with acute schizophrenia were randomized to receive brexpiprazole 0.25 mg/day ($N = 42$), 1 mg/day ($N = 89$), 2.5 mg/day ($N = 90$), 5 mg/day ($N = 93$), aripiprazole 15 mg/day ($N = 50$), or placebo ($N = 95$). Dose adjustments were permitted, with subjects randomized to 1 mg/day eligible to receive 0.5–1.5 mg/day, subjects randomized to 2.5 mg/day could receive 2–3 mg/day, and subjects randomized to 5 mg/day could receive 4–6 mg/day. Subjects randomized to aripiprazole could have their dose adjusted between 10 and 20 mg/day. Mean improvement in PANSS scores was clinically meaningful for all dose groups, including placebo. Improvements in the brexpiprazole (1, 2.5, and 5 mg) and aripiprazole treatment groups were numerically greater, but not significantly different from placebo.

The preliminary results of a phase II study examining brexpiprazole as an adjunct to antidepressants in the treatment of major depressive disorder are also available [93]. The study included a 6-week randomized period where 429 subjects who had exhibited inadequate response to antidepressant monotherapy were allocated to receive double-blind adjunctive brexpiprazole 0.15 mg/day ($N = 62$), 0.5 mg/day ($N = 120$), or 1.5 mg/day ($N = 121$), or adjunctive placebo ($N = 126$). Statistically significant improvements in mean MADRS total score, from baseline to endpoint, were observed only for subjects receiving adjunctive brexpiprazole at the 1.5 mg/day dose compared with placebo.

5.5.3 *Tolerability and Safety*

In the phase II schizophrenia study where preliminary information is available [92], commonly observed adverse reactions (incidence ≥5 % and twofold greater than placebo) were diarrhea (placebo 3.2 % versus brexpiprazole 0.25 mg/day 7.1 %, 1 mg/day 5.6 %, 2.5 mg/day 1.1 %, 5 mg/day 4.3 %, aripiprazole 8 %), nausea (placebo 2.1 % versus brexpiprazole 0.25 mg/day 2.4 %, 1 mg/day 4.5 %, 2.5 mg/day 7.8 %, 5 mg/day 6.5 %, aripiprazole 2 %), weight increased (placebo 3.2 % versus brexpiprazole 0.25 mg/day 2.4 %, 1 mg/day 6.7 %, 2.5 mg/day 10 %, 5 mg/day 6.5 %, aripiprazole 6 %), akathisia (placebo 4.2 % versus brexpiprazole 0.25 mg/day 2.4 %, 1 mg/day 6.7 %, 2.5 mg/day 5.6 %, 5 mg/day 15.1 %, aripiprazole 4 %), and agitation (placebo 4.2 % versus brexpiprazole 0.25 mg/day 9.5 %, 1 mg/day 4.5 %, 2.5 mg/day 4.4 %, 5 mg/day 7.5 %, aripiprazole 10 %). Mean weight change from baseline ranged from 0.5 to 1.4 kg, compared with 0.2 kg for placebo and 0.3 kg for aripiprazole. Proportions of patients with weight gain ≥7 % from baseline were 7.5, 7.3, 9.1, 11.1, 12, and 4 %, for placebo, brexpiprazole 0.25, 1, 2.5, 5 mg/day, and aripiprazole, respectively, resulting in values for NNH versus placebo of 62 (ns), 27 (ns), and 23 (ns) for brexpiprazole 1, 2.5, and 5 mg/day, respectively. No clinically relevant increases in the ECG QT interval or in prolactin levels were observed.

5.5.4 *Summary of Clinical Utility*

Brexpiprazole if approved would potentially be the third dopamine partial agonist available for the treatment of mental disorders. Insufficient information is available at present to assess clinical utility apart from the similarities it appears to have with aripiprazole.

5.6 Zicronapine

5.6.1 *Pharmacodynamics and Pharmacokinetics*

Zicronapine is in phase III of clinical development for the treatment of schizophrenia [94]. Very limited information about zicronapine is available publicly. A press release notes that zicronapine has potent antagonistic effects at dopamine D1, D2, and serotonin 5-HT2A receptors [57].

5.6.2 *Efficacy*

Two randomized phase II studies in acute schizophrenia have been reported in a press release [57]. In one study, approximately 280 subjects received blinded treatment with either zicronapine (3, 5, 7, and 10 mg/day) or placebo

for 8 weeks. Zicronapine 7 and 10 mg/day demonstrated superiority over placebo on the PANSS. In the second study, 93 patients were randomized to treatment with either flexible doses (5–7 mg/day) of zicronapine or flexible doses of olanzapine (10–15 mg/day) for 12 weeks. Zicronapine showed comparable reduction in PANSS score.

5.6.3 Tolerability and Safety

Detailed information is not publicly available. Press releases state that zicronapine is safe and well tolerated and that, in the olanzapine-referenced study, the number of withdrawals was similar to the level of withdrawals in the olanzapine group [57, 94].

5.6.4 Summary of Clinical Utility

Insufficient information is available at present to assess clinical utility. A 6-month phase III clinical trial enrolling approximately 160 patients with schizophrenia was recently completed (NCT01295372). Patients were randomized to zicronapine 7.5 mg/day or risperidone 5 mg/day [94]; results have not yet been presented. A study of once-weekly dosing of zicronapine (NCT01377233) has also been completed; results have not yet been presented.

5.7 Bitopertin

5.7.1 Pharmacodynamics and Pharmacokinetics

Bitopertin is a glycine transporter type 1 inhibitor currently in phase III of drug development for schizophrenia. Inhibition of the synaptic glycine reuptake pump is hypothesized to help alleviate the glutamate *N*-methyl-D-aspartate (NMDA) receptor hypofunctioning that may underlie dopamine dysregulation in individuals with schizophrenia [95, 96]. Bitopertin is thus different from all currently available antipsychotics whose mechanism of action is centered on dopamine D2 receptor antagonism or partial agonism.

In a positron emission tomography study in healthy volunteers, steady-state plasma concentrations increased in a dose-proportional manner [97]. In another study in healthy male volunteers, peak bitopertin plasma concentrations were achieved ~4 h after dosing and the terminal elimination half-life was ~53 h [98]. Bitopertin does not significantly inhibit the major drug-metabolizing CYP450 enzymes 3A4, 2D6, 2C9, 2C19, and 1A2 [99].

5.7.2 Efficacy

Preliminary results are available for one phase II, 8-week, double-blind, placebo-controlled trial [100] where 323 clinically stable schizophrenia patients with predominantly negative symptoms and low severity of positive symptoms were randomized to daily doses of 10, 30, and 60 mg of bitopertin added to ongoing second-generation antipsychotic medication treatment. The PANSS, CGI-I, and Personal and Social Performance (PSP) scales were used to measure negative symptom severity, overall symptom severity, and function. Overall, efficacy parameters were consistently improved in the 10-mg dose group, to a lesser extent in the 30-mg dose group, and not so in the 60-mg dose group. The negative symptom factor score from the PANSS demonstrated a significantly greater decrease from baseline in the 10- and 30-mg dose groups than in the placebo group in the per-protocol population ($N = 231$); the percentage of responders (≥20 % improvement from baseline on the negative symptom factor score) were 43, 65, 60, and 43 % for placebo, bitopertin 10, 30, and 60 mg/day, respectively, yielding an NNT versus placebo for bitopertin 10 mg/day of 5 (95 % CI 3–22). The percentages of patients rated as "much improved" or "very much improved" on the CGI-I for negative symptoms were statistically significantly higher for the 10-mg group versus placebo for the per-protocol population as well as the intent-to-treat population ($N = 312$). There was a trend towards functional improvement as evidenced by an increase in PSP score from baseline to week 8 in the 10-mg dose group versus placebo in the per-protocol population. The 60-mg dose group did not differ from placebo on any outcome measure.

5.7.3 Tolerability and Safety

In the phase II study described above [100], the percentage of patients discontinuing due to an adverse event was 1, 1, 9, and 10 %, for placebo, bitopertin 10, 30, and 60 mg/day, respectively, for an NNH versus placebo of 14 (95 % CI 8–121) and 12 (95 % CI 7–55) for bitopertin 30 and 60 mg/day, respectively. Hemoglobin levels were specifically monitored due to a known effect of glycine transport inhibition on heme synthesis in erythropoietic cells; proportions of patients with decreased hemoglobin were 4, 5, 10, and 21 % for placebo, bitopertin 10, 30, and 60 mg/day, respectively, for an NNH versus placebo of 100 (ns), 17 (ns), and 6 (95 % CI 4–15) for bitopertin 10, 30, and 60 mg/day, respectively. Commonly observed adverse reactions (incidence ≥5 % and twofold greater than placebo) were somnolence (3, 7, 5, 10 %, for placebo, bitopertin 10, 30, and 60 mg/day, respectively), dizziness (3, 1, 4, 12 %, respectively), and headache (1, 2, 2, 9 %, respectively); resultant NNH values versus placebo were all ns except for bitopertin 60 mg/day where NNH for somnolence was 13 (95 % CI 7–491), dizziness 12 (95 % CI 6–86), and headache 13 (95 % CI 7–108).

A dedicated ECG QT study of bitopertin in 169 healthy male volunteers is available [98]. In this randomized, double-blind, placebo-controlled, parallel-group study, doses of bitopertin included 30 and 175 mg/day. Moxifloxacin was used for assay sensitivity. The mean change in placebo-corrected QTcF from baseline to day 10 of bitopertin ranged from −2.8 to 3.9 ms. There was no relation between bitopertin concentrations and changes in QTcF or other ECG variables. Dizziness, nausea, and blurred vision were more common in the bitopertin 175-mg group than the bitopertin 30-mg or placebo groups.

5.7.4 Summary of Clinical Utility

Adjunctive bitopertin 10 mg/day appears efficacious in decreasing negative symptoms, with an NNT versus placebo of 5 (95 % CI 3–22), and was well tolerated at that dose. In contrast, bitopertin 60 mg/day did not appear efficacious and was associated with a greater rate of adverse events. Efficacy and safety results for bitopertin 10 mg/day up to 30 mg/day were considered promising, and several additional clinical trials are currently underway examining patients with suboptimally controlled symptoms of schizophrenia; persistent, predominant negative symptoms of schizophrenia; biomarker measures of cognitive dysfunction in patients with schizophrenia; and patients with acute exacerbation of schizophrenia (see http://www.clinicaltrials.gov). In most of these efficacy trials, bitopertin is administered adjunctively with antipsychotics.

5.8 EVP-6124

5.8.1 Pharmacodynamics and Pharmacokinetics

EVP-6124 is a selective alpha-7 nicotinic acetylcholine receptor agonist [56] and is currently in phase III of clinical development. Alpha-7 nicotinic acetylcholine receptors are located in several brain areas involved in various domains of cognition, including attention and long-term and working memory [56].

EVP-6124 dosed once a day is reported to exhibit linear kinetics, with a half-life of >60 h [56].

5.8.2 Efficacy

The putative pro-cognitive effects of EVP-6124 at 0.3 and 1 mg/day were tested in an 84-day phase II, randomized, double-blind, placebo-controlled study in 319 patients with chronic stable schizophrenia receiving second-generation antipsychotic therapy other than clozapine [56]. EVP-6124 had a positive effect on global cognitive function and on functionality, as well as on the PANSS negative subscale. There was no effect on the PANSS positive subscale.

5.8.3 Tolerability and Safety

EVP-6124 has been reported as safe and well tolerated in nine clinical studies in 561 unique subjects, where 403 received EVP-6124 and 158 received placebo [56]. In the reported phase II study, the drug was well tolerated; there were no clinically significant findings with respect to 12-lead ECGs, vital signs, hematology, and serum chemistry evaluations or suicidal ideation and behavior. The most commonly reported adverse events were headache (3.8 %), nausea (3.2 %), and nasopharyngitis (2.5 %).

5.8.4 Summary of Clinical Utility

Insufficient detailed information is available at present to assess clinical utility, but the adjunctive use of EVP-6124 appears promising.

6 Applying the Results

6.1 Examining Differences between Agents

6.1.1 Heterogeneity

It is clear that in clinical practice there is substantial inter-individual variation in therapeutic response when prescribing antipsychotic medication. Even though there may be advantages for efficacy for some antipsychotics over others when comparing groups of subjects in clinical trials, as illustrated by several meta-analyses [59–61], larger and more predictable differences exist between antipsychotic agents regarding their adverse effects, and these latter considerations often drive antipsychotic selection [4]. Adverse effects can have both tolerability and safety implications; although some overlap exists, tolerability will impact on a patient's willingness to take a medication, whereas safety concerns will impact on a prescriber's willingness to prescribe the offending agent. The most commonly associated adverse events observed with partial or non-adherence are weight gain, sedation/somnolence, akathisia, sexual dysfunction, parkinsonian symptoms, and cognitive problems [101]. Safety concerns on the part of clinicians have become focused on cardiovascular/cardiometabolic morbidity and mortality [102, 103].

6.1.2 Metabolic Variables

A meta-analysis is available that examines body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone, and paliperidone in the treatment of schizophrenia and bipolar disorder [34]. The authors did not

include cariprazine or other agents in clinical development. A total of 56 clinical trials were identified. In the short-term trials versus placebo, a ≥7 % weight increase was statistically significantly most prevalent for asenapine (five trials, $n = 1{,}360$, relative risk [RR] 4.09, 95 % CI 2.25–7.43, NNH 17), followed by iloperidone (four trials, $n = 1{,}931$, RR 3.13, 95 % CI 2.08–4.70, NNH 11) and paliperidone (12 trials, $n = 4{,}087$, RR 2.17, 95 % CI 1.64–2.86, NNH 20). The effect of lurasidone on body weight (six trials, $n = 1{,}793$, RR 1.42, 95 % CI 0.87–2.29) was not statistically significant. Using continuous measures, short-term weight gain was statistically significantly greater than placebo with iloperidone (one trial, $n = 300$, +2.50 kg, 95 % CI 1.92–3.08), paliperidone (15 trials, $n = 3{,}552$, +1.24 kg, 95 % CI 0.91–1.57), asenapine (three trials, $n = 751$, +1.16 kg, 95 % CI 0.83–1.49), as well as with lurasidone (five trials, $n = 999$, +0.49 kg, 95 % CI 0.17–0.81). Longer-term data versus placebo were only available for asenapine and paliperidone, demonstrating statistically significantly greater weight gain versus placebo for both asenapine (three trials, $n = 311$, +1.30 kg, 95 % CI 0.62–1.98) and paliperidone (six trials, $n = 1{,}174$, +0.50 kg, 95 % CI 0.22–0.78). The authors found no clinically meaningful differences of worsening for paliperidone, iloperidone, asenapine, or lurasidone versus placebo regarding the mean change from baseline to endpoint in cholesterol or triglyceride levels in short-term trials, with the possible exceptions of iloperidone for total cholesterol (one trial, $n = 300$, +11.60 mg/dL, 95 % CI 4.98–18.22), and LDL cholesterol (one trial, $n = 300$, +10.30 mg/dL, 95 % CI 4.94–15.66). Asenapine increased total cholesterol statistically significantly during longer-term treatment (one trial, $n = 194$, +6.53 mg/dL, 95 % CI 1.17, 11.89). Statistically significant elevations in glucose levels were noticed during short-term treatment with iloperidone (one trial, $n = 300$, +6.90 mg/dL, 95 % CI 2.48–11.32) and during long-term treatment with paliperidone (six trials, $n = 1022$, +3.39 mg/dL, 95 % CI 0.42–6.36). These data are consistent with data presented in product labeling and noted in Tables 4, 7, and 10 for iloperidone, asenapine, and lurasidone, respectively.

6.1.3 Weight Gain, Somnolence, and Akathisia

Placing iloperidone, asenapine, lurasidone, and asenapine in clinical context, these agents appear similar to aripiprazole [79] and ziprasidone [63, 104] in terms of their relative 'friendliness' regarding metabolic adverse outcomes compared with older second-generation antipsychotics such as olanzapine [105]. However, there is some variation among the 'metabolically friendlier' second-generation antipsychotics in terms of effects on body weight and perhaps some of the metabolic variables. Moreover, they vary a great deal in terms of other potential adverse effects (for example, somnolence, akathisia, effects on the ECG QT interval, effects on prolactin), as well as how they may be administered (differing requirements for initial titration, dosing frequency of once daily versus bid, administration with/without food, route of metabolism, and consequences for dosing and drug–drug interactions; see also Table 1). Table 13 provides a basis for indirect comparisons of the first-line oral second-generation antipsychotics (and cariprazine) regarding weight gain ≥7 % from baseline and the rate of spontaneously reported adverse events of somnolence or akathisia, using NNH versus placebo [76, 106–109]. The NNH values are provided separately for the FDA-approved (or pending) indications of schizophrenia, bipolar mania/mixed episodes, bipolar depression, and adjunctive use for major depressive disorder. In general, a single-digit NNH means that the adverse reaction can be expected commonly in day-to-day clinical practice. Single-digit NNH values versus placebo for weight gain are observed for olanzapine and quetiapine immediate release; for somnolence, quetiapine extended release, quetiapine immediate release, olanzapine, ziprasidone, and asenapine; and for akathisia, aripiprazole and cariprazine. If these adverse events are short lived, mild or moderate in intensity, or easily managed, then they may be essentially irrelevant. However, if an individual patient expresses a strong preference for avoiding certain adverse events, then no matter how mild or temporary these adverse events may be, these effects can significantly impact adherence. In addition, adverse effects such as somnolence can sometimes be seen as a potential advantage under certain circumstances, such as when managing acute agitation. Additional considerations include the time to onset of the adverse event versus time to onset of a therapeutic response—this may tip the decision in favor of using the medication if its value to the patient can be demonstrated quickly. A caveat about these indirect comparisons is that the NNH values are calculated from pooled study results for each medication, and that the study populations themselves may differ in unknown but important ways, as well as differ from patients we would ordinarily treat in clinical practice. In addition, the intensity and duration of adverse reactions to medications are not adequately captured by relying only on the spontaneous reporting of adverse events. Thus, direct comparisons using an appropriately designed clinical trial would yield more precise information.

6.2 Medication Selection

There is no guarantee that a specific medication will be efficacious or that a particular adverse event will or will not

Table 13 Number needed to harm at a glance: number needed to harm versus placebo for first-line oral second-generation antipsychotics in adults for weight gain, somnolence, and akathisia, observed in acute short-term studies, all doses pooled, by approved (or pending) indication[a]

Antipsychotic	NNH (95 % CI) for weight gain ≥7 % from baseline				NNH (95 % CI) for somnolence adverse events				NNH (95 % CI) for akathisia adverse events			
	Schizophrenia	Bipolar mania	Bipolar depression	Adjunctive for MDD	Schizophrenia	Bipolar mania	Bipolar depression	Adjunctive for MDD	Schizophrenia	Bipolar mania	Bipolar depression	Adjunctive for MDD
Risperidone	12 (na)	1,000 (na)			17 (12–33)	34 (19–172)			15 (10–32)	17 (12–34)		
Olanzapine	6 (na) (SCZ and BM)		6 (4–10)	3 (3–3)	7 (5–10) (SCZ and BM)		12 (ns)	11 (8–21)	25 (14–134)	NA	NA	167 (ns)
Quetiapine IR	6 (5–9)	8 (na)	17 (12–32)		10 (8–17) (SCZ and BM)		3 (3–3)		ND	ND	34 (21–83)	
Quetiapine XR	22 (13–74)	20 (12–71)	14 (8–50)	29 (18–79)	7 (6–10)	3 (3–4)	3 (2–4)	4 (3–4)	188 (ns)	143 (ns)	69 (ns)	91 (ns)
Ziprasidone	17 (na)	NA			15 (10–33)	6 (4–9)			100 (ns)	20 (ns)		
Aripiprazole	20 (na)	ND		24 (17–45)	20 (na) (SCZ and BM)			50 (ns)	25 (16–70)	12 (9–16)		6 (5–7)
Paliperidone	35 (ns)				42 (ns)				39 (ns)			
Iloperidone	10 (8–13)				16 (11–27)				ND			
Asenapine	35 (20–132)	19 (13–37)			17 (11–43)	6 (5–9)			34 (18–249)	50 (ns)		
Lurasidone	67 (ns)		59 (ns)		11 (8–14)		25 (ns)		10 (9–13)		15 (10–33)	
Cariprazine	19 (10–112)	NA			NA	23 (12–274)			8 (6–12)	6 (4–10)		

[a] Data from Citrome [106–109], calculated from Loebel et al. [76], or extracted from applicable product labels if not available from the author's published work; whenever the same NNH is reported for more than one disease state for one particular agent, this is because data in the product label were reported for the pooled populations; data for akathisia and somnolence for risperidone are for doses 2–8 mg/day; for bipolar depression and adjunctive use for MDD, data for olanzapine are for the combination of olanzapine with fluoxetine; for lurasidone and bipolar depression, data are from the monotherapy trial; for cariprazine, data are from the available phase III trials

BM bipolar mania, *CI* confidence interval, *IR* immediate release, *MDD* major depressive disorder, *na* CI not calculable as the denominators were not provided for the incidence of interest in the product label, *NA* not available (for product labels, the incidence of the adverse event in question may not have reached the reporting threshold), *ND* no difference—rate same or lower for antipsychotic than placebo, *NNH* number needed to harm, *ns* not statistically significant (the 95 % CI encompasses infinity), *SCZ* schizophrenia, *XR* extended release

occur in a specific individual. Patient preference can help guide medication choice if individual patients have specific concerns about certain adverse effects, such as weight gain, somnolence, and akathisia. Prolongation of the ECG QT interval is largely irrelevant in routine practice with reasonably healthy patients; initial concerns regarding the risk for QT prolongation with ziprasidone has not materialized in clinically significant arrhythmias [63].

Guidelines for treatment can also be helpful in medication selection, and examples include those available through the World Federation of Societies of Biological Psychiatry [110–114]. A 'guideline of guidelines' for the treatment of schizophrenia, which includes the use of iloperidone, asenapine, and lurasidone, is also available [115]. Additional meta-analytical studies are becoming available that include the newer antipsychotics [116]; however, due caution is required as heterogeneity in effects in individual patients is considerable.

7 Assessing Outcomes

Step number 5 of the five-step EBM process (Fig. 1) behooves the clinician to circle back and ensure that the research evidence being used in the medical decision-making process is of sufficient quality to rely on and consistent with the goals of treatment for that individual patient. Step 5 also includes the need to measure the patient outcome and to validate it. The BPRS or PANSS are too lengthy to be used in routine care in most clinical settings and the focus on psychopathology alone may divert attention away from other important outcomes such as personal and social functioning. However, the CGI-Severity (CGI-S) scale [117] is suitable for day-to-day use (see Fig. 2); it consists of one item, is clinically intuitive, and can easily be incorporated in routine record keeping without any additional time burden. Moreover, the CGI-S correlates well with the BPRS [118] and PANSS [119].

8 Conclusions

Choosing among all the different antipsychotics for an individual patient is complex, requiring consideration of the prior history of therapeutic response, prior history of tolerability with other agents, and individual patient values and preferences. Ultimately, heterogeneity in individual response in the clinic trumps differences found between groups of patients in clinical trials. Patients may also have specific sensitivities to certain adverse effects of medication, such as akathisia, sedation, or weight gain. Having different options in order to optimize efficacy and tolerability for the individual patient is desirable.

Three new second-generation antipsychotics are available: iloperidone, asenapine, and lurasidone. Cariprazine is expected in the near future. Similar to ziprasidone and aripiprazole, these new agents have a lower propensity for weight gain and metabolic abnormalities than older second-generation antipsychotics such as olanzapine; lurasidone appears to be best in class in terms of minimizing untoward alterations in body weight and metabolic variables. However, iloperidone, asenapine, lurasidone, and cariprazine differ among themselves in terms of on-label dosing frequency (once daily for lurasidone and, presumably, cariprazine, versus twice daily for iloperidone and asenapine), the need for initial titration to a therapeutic dose for iloperidone and possibly cariprazine, requirement to be taken sublingually for asenapine, requirement for administration with food for lurasidone, lengthening of the ECG QT interval (greater for iloperidone than for asenapine and no effect observed with lurasidone), and adverse effects such as akathisia (seen with cariprazine, lurasidone, and asenapine but not with iloperidone) and sedation (most notable with asenapine). In addition to cariprazine, other agents are in phase III of clinical development but have not yet been submitted for FDA approval, and there is insufficient information publically available at this time to make any quantitative conclusions about their place in therapy. These include two additional second-generation antipsychotics that target the dopamine D2 receptor, brexpiprazole (partial agonist) and zicronapine (antagonist), and two other agents with completely different mechanisms of action, bitopertin (a glycine transporter type 1 inhibitor that impacts on the glutamate NMDA receptor) and EVP-6124 (an agonist at the alpha-7 nicotinic acetylcholine receptor). Both bitopertin and EVP-6124 are being tested principally as adjunctive agents to second-generation antipsychotics

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

Fig. 2 Clinical Global Impressions-Severity (CGI-S). This scale is in the public domain. See Guy [117]

for specific treatment domains, including negative and cognitive symptoms.

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References

1. Citrome L. Evidence-based medicine: it's not just about the evidence. Int J Clin Pract. 2011;65(6):634–5.
2. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312(7023):71–2.
3. Citrome L, Ketter TA. Teaching the philosophy and tools of evidence-based medicine: misunderstandings and solutions. Int J Clin Pract. 2009;63(3):353–9.
4. Volavka J, Citrome L. Oral antipsychotics for the treatment of schizophrenia: heterogeneity in efficacy and tolerability should drive decision-making. Expert Opin Pharmacother. 2009;10(12):1917–28.
5. Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand. 2008;117(6):412–9.
6. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract. 2013;67(5):407–11.
7. Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol. 2008;28(2 Suppl 1):S20–8.
8. Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol. 2008;28(2 Suppl 1):S4–11.
9. Weiden PJ, Cutler AJ, Polymeropoulos MH, et al. Safety profile of iloperidone: a pooled analysis of 6-week acute-Phase pivotal trials. J Clin Psychopharmacol. 2008;28(2 Suppl 1):S12–9.
10. Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol. 2008;28(2 Suppl 1):S29–35.
11. Cutler AJ, Kalali AH, Mattingly GW, et al. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. CNS Spectr. 2013;18(1):43–54.
12. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry. 2007;68(10):1492–500.
13. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30(2):106–15.
14. Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. J Clin Psychiatry. 2011;72(3):349–55.
15. Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of Asenapine vs. Olanzapine in patients with schizophrenia or schizoaffective disorder. Pharmacopsychiatry. 2010;43(4):138–46.
16. Schoemaker J, Stet L, Vrijland P, et al. Long-term efficacy and safety of asenapine or olanzapine in patients with schizophrenia or schizoaffective disorder: an extension study. Pharmacopsychiatry. 2012;45(5):196–203.
17. Buchanan RW, Panagides J, Zhao J, et al. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. J Clin Psychopharmacol. 2012;32(1):36–45.
18. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. Bipolar Disord. 2009;11(7):673–86.
19. McIntyre RS, Cohen M, Zhao J, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord. 2009;11(8):815–26.
20. McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord. 2010;126(3):358–65.
21. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Affect Disord. 2010;122(1–2):27–38.
22. Szegedi A, Calabrese JR, Stet L, et al. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. J Clin Psychopharmacol. 2012;32(1):46–55.
23. Ogasa M, Kimura T, Nakamura M, et al. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology (Berl). 2013;225(3):519–30.
24. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(6):829–36.
25. Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013;47(5):670–7.
26. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011;168(9):957–67.
27. Stahl SM, Cucchiaro J, Simonelli D, et al. Effectiveness of lurasidone for patients with schizophrenia following 6 weeks of acute treatment with lurasidone, olanzapine, or placebo: a 6-month, open-label, extension study. J Clin Psychiatry. 2013;74(5):507-15
28. McEvoy JP, Citrome L, Hernandez D, et al. Effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: a randomized, 6-week, open-label study. J Clin Psychiatry. 2013;74(2):170–9.
29. Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res. 2013;145(1–3):101–9.
30. Citrome L, Cucchiaro J, Sarma K, et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. Int Clin Psychopharmacol. 2012;27(3):165–76.
31. Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. Schizophr Res. 2011;132(2–3):101–7.
32. Harvey PD, Ogasa M, Cucchiaro J, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone. Schizophr Res. 2011;127(1–3):188–94.

33. Szegedi A, Verweij P, van Duijnhoven W, et al. Meta-analyses of the efficacy of asenapine for acute schizophrenia: comparisons with placebo and other antipsychotics. J Clin Psychiatry. 2012;73(12):1533–40.
34. De Hert M, Yu W, Detraux J, et al. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. CNS Drugs. 2012;26(9):733–59.
35. Citrome L. Oral antipsychotic update: a brief review of new and investigational agents for the treatment of schizophrenia. CNS Spectr. 2012;17(Suppl 1):1–9.
36. Citrome L. Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. Adv Ther. 2013;30(2):114–26.
37. Citrome L. Cariprazine in bipolar disorder: clinical efficacy, tolerability, and place in therapy. Adv Ther. 2013;30(2):102–13.
38. Citrome L. Cariprazine : chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety, and tolerability. Expert Opin Drug Metab Toxicol. 2013;9(2):193–206.
39. Citrome L. Lurasidone in schizophrenia: new information about dosage and place in therapy. Adv Ther. 2012;29(10):815–25.
40. Citrome L. Lurasidone for the acute treatment of adults with schizophrenia: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? Clin Schizophr Relat Psychoses. 2012;6(2):76–85.
41. Kantrowitz JT, Citrome L. Lurasidone for schizophrenia: what's different? Expert Rev Neurother. 2012;12(3):265–73.
42. Citrome L. Iloperidone: a clinical overview. J Clin Psychiatry. 2011;72(Suppl 1):19–23.
43. Citrome L, Meng X, Hochfeld M, et al. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four Phase III, placebo- and active-controlled trials. Hum Psychopharmacol. 2012;27(1):24–32.
44. Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. Schizophr Res. 2011;131(1–3):75–81.
45. Citrome L. Role of sublingual asenapine in treatment of schizophrenia. Neuropsychiatr Dis Treat. 2011;7:325–39.
46. Citrome L. Iloperidone, asenapine, and lurasidone: a brief overview of 3 new second-generation antipsychotics. Postgrad Med. 2011;123(2):153–62.
47. Citrome L. Lurasidone for schizophrenia: a brief review of a new second-generation antipsychotic. Clin Schizophr Relat Psychoses. 2011;4(4):251–7.
48. Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract. 2011;65(2):189–210.
49. Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. Expert Opin Drug Metab Toxicol. 2010;6(12):1551–64.
50. Citrome L. Iloperidone redux: a dissection of the Drug Approval Package for this newly commercialised second-generation antipsychotic. Int J Clin Pract. 2010;64(6):707–18.
51. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. Int J Clin Pract. 2009;63(12):1762–84.
52. Citrome L. Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialised second-generation antipsychotic. Int J Clin Pract. 2009;63(8):1237–48.
53. Novartis Pharmaceuticals Corporation. Fanapt (iloperidone) tablets. Product label. January 2013. http://www.pharma.us.novartis.com/product/pi/pdf/fanapt.pdf. Accessed 7 April 2013.
54. Merck & Co., Inc. Saphris (asenapine) sublingual tablets. Product label. March 2013. http://www.merck.com/product/usa/pi_circulars/s/saphris/saphris_pi.pdf. Accessed 7 April 2013.
55. Sunovion Pharmaceuticals Inc. Latuda (lurasidone hydrochloride) tablets. Product label. July 2013. http://www.latuda.com/LatudaPrescribingInformation.pdf. Accessed 14 August 2013.
56. Meltzer HY, Gawryl M, Ward S, et al. EVP-6124, an alpha-7 nicotinic partial agonist, produces positive effects on cognition, clinical function, and negative symptoms in patients with chronic schizophrenia on stable antipsychotic therapy. Neuropsychopharmacology. 2011;36(Suppl):S170–1.
57. Lundbeck H, A/S. Zicronapine shows significant positive data in clinical phase II in the treatment of patients with schizophrenia – planning for continued clinical work. Press release No. 392 18 December 2009. http://investor.lundbeck.com/releasedetail.cfm?ReleaseID=608605. Accessed 17 April 2013.
58. Shayegan DK, Stahl SM. Atypical antipsychotics: matching receptor profile to individual patient's clinical profile. CNS Spectr. 2004;9(Suppl. 11):6–14.
59. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31–41.
60. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166(2):152–63.
61. Leucht S, Arbter D, Engel RR, et al. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol Psychiatry. 2009;14(4):429–47.
62. Pfizer Inc. Geodon (ziprasidone HCl) capsules. Product label. March 2013. http://labeling.pfizer.com/ShowLabeling.aspx?id=584. Accessed 9 April 2013.
63. Citrome L. Drug safety evaluation of ziprasidone. Expert Opin Drug Saf. 2011;10(3):437–48.
64. Potkin SG, Preskorn S, Hochfeld M, et al. A Thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. J Clin Psychopharmacol. 2013;33(1):3–10.
65. United States Food and Drug Administration. Saphris (Asenapine) Sublingual Tablets. Briefing Book. 30 July 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173877.pdf. Accessed 9 April 2013.
66. Schering-Plough Research Institute. Saphris (Asenapine) Sublingual Tablets. Briefing Document (Background Package). 30 July 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173876.pdf. Accessed 9 April 2013.
67. Ballaz SJ, Akil H, Watson SJ. The 5-HT7 receptor: role in novel object discrimination and relation to novelty-seeking behavior. Neuroscience. 2007;149(1):192–202.
68. Chapel S, Hutmacher MM, Haig G, et al. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. J Clin Pharmacol. 2009;49(11):1297–308.
69. Blier P, Ward NM. Is there a role for 5-HT1A agonists in the treatment of depression? Biol Psychiatry. 2003;53(3):193–203.
70. Ohno Y. Therapeutic role of 5-HT1A receptors in the treatment of schizophrenia and Parkinson's disease. CNS Neurosci Ther. 2011;17(1):58–65.
71. Citrome L. Using oral ziprasidone effectively: the food effect and dose-response. Adv Ther. 2009;26(8):739–48.
72. United States Food and Drug Administration. Drug Approval Package. Latuda (lurasidone hydrochloride) Tablets. 3 December 2010. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200603Orig1s000TOC.cfm. Accessed 10 April 2013.

73. Dainippon Sumitomo Pharma. Dainippon Sumitomo Pharma announces Pan-Asia study results for lurasidone, an atypical antipsychotic agent, in the treatment of schizophrenia. Press Release 11 May 2011. http://www.ds-pharma.com/news/pdf/ene20110511_3.pdf. Accessed 10 April 2013.
74. Loebel A, Cucchiaro J, Xu J, et al. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, noninferiority study. Schizophr Res. 2013;147(1):95-102
75. Silva R, Correll C, Simonelli D, et al. Long-term safety and effectiveness of lurasidone in schizophrenia: results of a 22-month, open-label extension study. Poster Presentation NR6-37; American Psychiatric Association 165th Annual Meeting; May 5–9, 2012; Philadelphia, Pennsylvania.
76. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy for the treatment of bipolar I depression: results of a 6-week, double-blind, placebo-controlled study. Poster Presentation NR4-58; American Psychiatric Association; 165th Annual Meeting; May 5–9, 2012; Philadelphia, Pennsylvania.
77. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone adjunctive to lithium or valproate for the treatment of bipolar I depression: results of a 6-week, double-blind, placebo-controlled study. Poster Presentation NR4-29; American Psychiatric Association; 165th Annual Meeting; May 5–9, 2012; Philadelphia, Pennsylvania.
78. Sunovion Pharmaceuticals Inc. Sunovion Pharmaceuticals Announces FDA Approval of Latuda® (lurasidone HCl) as Monotherapy and Adjunctive Therapy in Adult Patients with Bipolar Depression. Press release 28 June 2013. http://www.ds-pharma.com/pdf_view.php?id=306. Accessed 10 July 2013.
79. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. Neuropsychiatr Dis Treat. 2006;2(4):427–43.
80. Gyertyan I, Kiss B, Saghy K, et al. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochem Int. 2011;59(6): 925–35.
81. Litman R, Papadakis K, Durgam S, et al. Use of cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Poster Presentation 61; 60th Institute on Psychiatric Services of the American Psychiatric Association; October 2–5, 2008; Chicago, IL.
82. Bose A, Li D, Migliore R, et al. The efficacy and safety of the novel antipsychotic cariprazine in acute exacerbation of schizophrenia. Poster Presentation I-73; NCDEU 50th Annual Meeting; June 14–17, 2010; Boca Raton, Florida.
83. Zukin, SR, Kane J, Cutler, AJ, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: a phase III, international, randomized, double-blind, placebo-controlled trial. Poster Presentation W9; American College of Neuropsychopharmacology 51st Annual Meeting; December 2–6, 2012; Hollywood, Florida.
84. Forest Laboratories, Inc. and Gedeon Richter Plc. Announce Results from Two Positive Phase III Trials with the Investigational Antipsychotic Cariprazine for the Treatment of Schizophrenia [press release]. Forest Laboratories, Inc.; 28 Feb 2012. http://news.frx.com/press-release/rd-news/forestlaboratoriesinc-and-gedeon-richter-plc-announceresultstwo-positive-p. Accessed 16 April 2013.
85. Knesevich MA, Papadakis K, Bose A, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar disorder: a Phase II trial. Poster Presentation NR1-49; American Psychiatric Association 162nd Annual Meeting; 16–21 May 2009; San Francisco, California.
86. Starace A, Bose A, Wang Q, et al. Cariprazine in the treatment of acute mania in bipolar disorder: a double-blind, placebo-controlled, Phase III trial. Poster Presentation NR9-42; American Psychiatric Association 165th Annual Meeting; 5–9 May 2012;Philadelphia, Pennsylvania.
87. Forest Laboratories, Inc. and Gedeon Richter Plc announce positive phase III results with the investigational antipsychotic cariprazine in patients with acute mania associated with bipolar I disorder [press release]. Forest Laboratories, Inc.; 8 Feb 2012. http://news.frx.com/press-release/product-news/forest-laboratories-inc-and-gedeon-richter-plcannouncepositive-phase-ii. Accessed 16 April 2013.
88. Cutler A, Bose A, Durgam S, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week extension study. Poster Presentation NR6-50; American Psychiatric Association 165th Annual Meeting; 5–9 May 2012; Philadelphia, Pennsylvania.
89. Forest Laboratories, Inc. and Gedeon Richter Plc announce results from a phase II study of cariprazine for the treatment of bipolar depression [press release]. Forest Laboratories, Inc.; 30 Aug 2010. http://news.frx.com/press-release/rd-news/forest-laboratories-inc-and-gedeon-richterplcannounce-results-phase-ii-stu-0. Accessed 16 April 2013.
90. Forest Laboratories, Inc. Forest Laboratories, Inc. and Gedeon Richter Plc. Announce results from a phase II study of cariprazine as adjunctive therapy in major depressive disorder. Press Release. 28 Feb 2011. http://news.frx.com/press-release/rd-news/forest-laboratories-inc-andgedeon-richter-plc-announce-resultsphase-ii-study. Accessed 16 April 2013.
91. Kikuchi T, Maeda K, Sugino, et al. Preclinical pharmacology of OPC-34712: a novel compound with dopamine D2 receptor partial agonist activity. Poster presentation; Society of Biological Psychiatry 66th Annual Meeting; May 12–14, 2011; San Francisco, California.
92. McQuade R, Hobart M, Forbes RA, et al. A Phase II trial assessing the efficacy and safety of OPC-34712 in the acute treatment of adult schizophrenia (Study 331-07-203). Poster Presentation 140; 2011 US Psychiatric Congress; 7–10 Nov 2011.
93. Thase M, Fava M, Hobart M, et al. Efficacy and safety of adjunctive OPC-34712 in major depressive disorder: a Phase II, randomized, placebo-controlled study. Poster Presentation NR4-65; American Psychiatric Association 164th Annual Meeting; 14–18 May 2011; Honolulu, Hawaii.
94. Lundbeck H. A/S. The clinical phase III programme commenced on zicronapine. 20 Jan 2011. http://investor.lundbeck.com/releasedetail.cfm?ReleaseID=608573. Accessed 7 April 2013.
95. Alberati D, Moreau JL, Lengyel J, et al. Glycine reuptake inhibitor RG1678: a pharmacological characterization of an investigational agent for the treatment of schizophrenia. Neuropharmacology. 2012;62(2):1152–61.
96. Kantrowitz J, Javitt DC. Glutamatergic transmission in schizophrenia: from basic research to clinical practice. Curr Opin Psychiatry. 2012;25(2):96–102.
97. Martin-Facklam M, Pizzagalli F, Zhou Y, et al. Glycine transporter type 1 occupancy by bitopertin: a positron emission tomography study in healthy volunteers. Neuropsychopharmacology. 2013;38(3):504–12.
98. Hofmann C, Banken L, Hahn M, et al. Evaluation of the effects of bitopertin (RG1678) on cardiac repolarization: a thorough corrected QT study in healthy male volunteers. Clin Ther. 2012;34(10):2061–71.
99. Pinard E, Alanine A, Alberati D, et al. Selective GlyT1 inhibitors: discovery of [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), a promising novel medicine to treat schizophrenia. J Med Chem. 2010;53(12): 4603–14.

100. Umbricht D, Yoo K, Youssef E, et al. Glycine transporter type 1 (GlyT1) inhibitor RG1678: positive results of the proof-of-concept study for the treatment of negative symptoms in schizophrenia. Neuropsychopharmacology. 2010;35(Suppl):S320–1.
101. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70(Suppl 4):1–46.
102. Newcomer JW, Nasrallah HA, Loebel AD. The atypical antipsychotic therapy and metabolic issues national survey. J Clin Psychopharmacol. 2004;24(Suppl 1):S1–6.
103. Markowitz M, Levitan B, Mohammed AF, et al. Psychiatrists' preferences for benefit and risk outcomes and formulation in schizophrenia treatments: a conjoint analysis study. Poster Presentation (PS5-05); American Psychiatric Association 64th Institute on Psychiatric Services; October 2–7, 2012; New York City, New York.
104. Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. CNS Drug Rev. 2007;13(2):137–77.
105. Citrome L, Holt RI, Walker DJ, et al. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. Clin Drug Investig. 2011; 31(7):455–82.
106. Citrome L, Nasrallah HA. On-label on the table: what the package insert informs us about the tolerability profile of oral atypical antipsychotics, and what it does not. Expert Opin Pharmacother. 2012;13(11):1599–613.
107. Citrome L. Quantifying risk: the role of absolute and relative measures in interpreting risk of adverse reactions from product labels of antipsychotic medications. Curr Drug Saf. 2009;4(3): 229–37.
108. Citrome L. Adjunctive aripiprazole, olanzapine, or quetiapine for major depressive disorder: an analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Postgrad Med. 2010;122(4):39–48.
109. Citrome L. Olanzapine-fluoxetine combination for the treatment of bipolar depression. Expert Opin Pharmacother. 2011;12(17): 2751–8.
110. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2012;13(5): 318–78.
111. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013;14(1):2–44.
112. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14(3):154–219.
113. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry. 2010;11(2):81–109.
114. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry. 2009;10(2): 85–116.
115. Stahl SM, Morrissette DA, Citrome L, et al. "Meta-guidelines" for the management of patients with schizophrenia. CNS Spectr. 2013;18(3):150–62.
116. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013 (Epub ahead of print).
117. Guy W. EDCEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338). Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976:534–7.
118. Leucht S, Engel RR. The relative sensitivity of the Clinical Global Impressions Scale and the Brief Psychiatric Rating Scale in antipsychotic drug trials. Neuropsychopharmacology. 2006; 31(2):406–12.
119. Levine SZ, Rabinowitz J, Engel R, et al. Extrapolation between measures of symptom severity and change: an examination of the PANSS and CGI. Schizophr Res. 2008;98(1–3):318–22.