REVIEW

Iloperidone in the treatment of schizophrenia: an evidence-based review of its place in therapy

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Introduction: Schizophrenia is a chronic and debilitating mental disorder that affects the patient's and their family's quality of life, as well as financial costs and health care settings. Despite the variety of available antipsychotics, optimal treatment outcomes are not always achieved. Novel drugs, such as iloperidone, can provide more effective, tolerable and safer strategies.

Aim: To review the evidence for the clinical impact of iloperidone on the treatment of patients with schizophrenia.

Evidence review: Clinical trials, observational studies and meta-analyses reached a common consensus that iloperidone is as effective as haloperidol, risperidone and ziprasidone in reducing schizophrenia symptoms. Similar amounts of adverse events and discontinuations were observed with iloperidone compared to placebo and active treatments. Common adverse events are mild and include dizziness, hypotension, dry mouth and weight gain. Iloperidone can induce extension of QTc interval, and clinicians should be aware of its contraindications. In long-term trials, iloperidone also showed promising safety and tolerability profiles. The low propensity to cause akathisia, extrapyramidal symptoms (EPS), increased prolactin levels or changes to metabolic laboratory parameters support its use in practice. Results showed that iloperidone prevents relapse in stabilized patients, with a time to relapse superior to placebo and similar to haloperidol. Patients using a prior antipsychotic (eg, risperidone and aripiprazole) can easily switch to iloperidone with no serious impact on safety or efficacy. However, the acquisition costs of iloperidone may hamper its use. Further evidence comparing iloperidone with other antipsychotics, and pharmacoeconomic studies would be welcome.

Place in therapy: Considering just the clinical profile of iloperidone, it represents a promising drug for treating schizophrenia, particularly in patients who are intolerant to previous antipsychotics, as well as being suitable as first-line therapy. Cost-effectiveness comparisons are needed to justify its use in clinical practice.

Keywords: iloperidone, schizophrenia, clinical practice, evidence-based

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Core evidence clinical impact summary for iloperidone in schizophrenia

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Schizophrenia pathophysiology and iloperidone mechanism of action	From clinical trials and observational studies: moderate	Iloperidone arises as a potential alternative to treat schizophrenia. However, since the pathophysiology of the disease is not fully elucidated, there are some gaps in the literature concerning drugs activities.
		(Continued)

(Continued) Outcome measure	Evidence	Implications
Iloperidone as therapeutic choice	From clinical trials, observational studies and meta-analyses: clear	Iloperidone is an optimal alternative as monotherapy for the treatment of schizophrenia, due its proven efficacy and promising safety profile, particularly for patients who are intolerant to prior treatments.
Patient-oriented evidence		
Reduction in positive and negative symptoms: acute efficacy	From clinical trials and meta-analyses: clear	Iloperidone was more effective than placebo and similar to haloperidol, risperidone and ziprasidone in several psychometric scales and in symptoms assessment.
Maintenance of effectiveness and safety	From clinical long-term trials: clear	Iloperidone proved to have long-term efficacy and favorable safety profile compared to placebo and haloperidol.
Prevention of relapse in stabilized patients	From clinical trials: moderate	Few studies have evaluated this outcome. Iloperidone is better than placebo and equivalent to haloperidol in time to relapse.
Adverse events	From clinical trials, observational studies and meta-analyses: clear	Iloperidone is an alternative to avoid elevation in EPS and prolactin levels. The incidence of weight gain and other side effects (dizziness, orthostatic hypotension, dry mouth, sedation, extension of QTc interval) are common but can be prevented by drug titration and monitoring.
Adherence with treatment	From clinical trials, observational studies and meta-analyses: moderate	Some patients may discontinue treatment due to adverse events or inefficacy. However, drugs seem to be well tolerated among patients, especially for long periods.
Effectiveness in treatment-resistant schizophrenia	From clinical trials: insufficient	Clozapine remains the therapeutic option for treating resistant schizophrenia.
Economic evidence		
	Pharmacoeconomic studies: insufficient	No formal cost-effectiveness analysis has been conducted.

Scope, aim and objectives

Iloperidone (Fanapt®, Zomaril®) is an atypical antipsychotic, whose primary mechanism of action is the antagonism of certain receptors, such as dopamine D2 and serotonin 5-hydroxytryptamine (5HT) receptor 2A. Iloperidone was recently approved in the US for treating schizophrenia, became available in the market from early 2010, and is currently under evaluation for approval in Europe. This antipsychotic is being promoted due to its promising efficacy and safety profile compared to other therapeutic options available worldwide. The choice of a specific drug should be based on individual preference, prior treatment response, clinical risk factors and adherence history.

Since there are some published studies that assessed potential effects of iloperidone in patients with schizophrenia, it is valuable to gather all available information to provide a broader view over this topic, thus increasing the precision estimate of results and contributing toward clinical decision-making.

The objective of this review was to assess the impact of iloperidone on the treatment of schizophrenia and establish, where possible, its place in therapy, highlighting the advantages and disadvantages of this drug for clinical practice.

Methods
Search and eligibility criteria of studies for clinical and economic evidence

A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane Collaboration recommendations.[1,2]
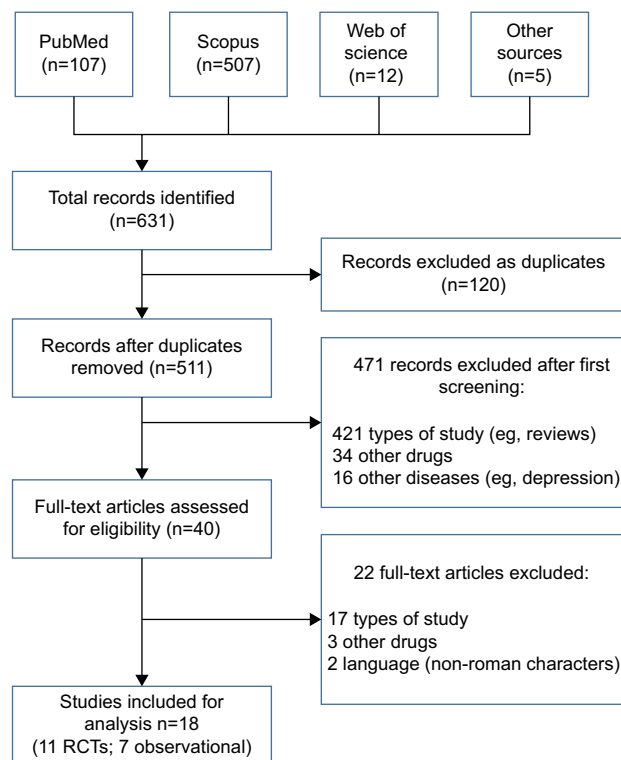
Figure 1 Flowchart of the systematic review process and final included studies.
Abbreviation: RCTs, randomized controlled trials.

Two reviewers performed all steps individually before reaching a consensus (FST and AW). Discrepancies were decided by a third author (FFL). We searched for articles in the following electronic databases without limits for time frame or language (updated in September 2016):

- PubMed, www.ncbi.nlm.gov
- Scopus, www.scopus.com
- Web of Science, www.webofscience.com
  Additional sources and the reference lists of the included studies were also consulted:
- National Institute for Health and Clinical Excellence (NICE), www.nice.org.uk
- Database of Abstracts of Reviews of Effects (DARE), National Health Service (NHS) Economic Evaluation Database (NHSEED), Health Technology Assessment (HTA), www.york.ac.uk/inst/crd/darehp.htm
- Clinical trial registries, www.clinicaltrials.gov

The following search terms were employed, together with Boolean operators AND or OR: iloperidone; Fanapt; Zomaril; HP-873; schizophrenia, schizophrenic*; dementia. We included studies assessing the drug intervention iloperidone alone or in combination with other pharmacological or non-pharmacological interventions, regardless of dosage, in patients diagnosed with any stage of schizophrenia and/or

related psychiatric disorders (no restriction of gender or age). For clinical evidence on the health-related outcomes of iloperidone, we primarily considered two types of studies: experimental trials (randomized clinical trials [RCTs] and extension studies) and observational studies (eg, case report and case series). Collected data were related to efficacy/effectiveness of iloperidone (eg, drug response, psychometric scales assessment), its tolerability and safety-related outcomes (eg, adverse events). The flowchart of the systematic review process (records identified, included and excluded registers and reasons for exclusions) is shown in Figure 1.

Results
Overview of the disease

Schizophrenia is a chronic, debilitating and complex mental disorder with a heterogeneous and multifactorial pattern caused by different genetic, epigenetic, developmental and environmental risk factors. There are challenges to fully understand the causes and pathogenesis of this disorder and to develop new, effective and acceptable treatments.[3,4]

Psychosis corresponds to the most familiar cluster of the positive symptoms of schizophrenia, which may include hallucinations, delusions and thought or movement disorders. The positive symptoms tend to relapse and remit, although some patients have residual long-term psychotic symptoms.[5,6] Negative symptoms are associated with disruptions to normal emotions and behaviors (eg, flat affect and poverty of speech). These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions.[3,5,7] For some people, cognitive symptoms may appear as poor executive functioning, difficulty focusing and problems with working memory.[8–10]

Diagnosis of schizophrenia usually occurs in young adults, based on symptoms outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), and is not usually associated with laboratory results.[7,8] To meet the criteria for diagnosis, the patient must have experienced at least two of the positive and/or negative symptoms, with at least one of the symptoms being delusions, hallucinations or disorganized speech. Continuous signs of the disturbance must persist for at least 6 months to be associated with marked impairment of functioning and not be better explained by another clinical condition. Early diagnosis is important to reduce the risk of a full-blown episode already in a premorbid stage or the risk of an impending relapse.[3,6,7]

The median incidence of schizophrenia in general population is ~1%, with 15.2 per 100,000 persons affected.[11,12] This disorder affects both genders equally, despite being prone to

occur earlier in men, and the effects can be long term and pervasive, with relapse being common. Although some variation by race or ethnicity has been reported, no racial differences in the prevalence of schizophrenia have been positively identified.[12,13] The first episode of psychosis usually occurs in late adolescence or early adulthood, but it is frequently preceded by a prodromal phase or a so-called at-risk mental state.[4,13]

Worldwide, schizophrenia falls into the top 10 medical disorders causing disability, and, apart from personal distress, this disease has a huge socioeconomic burden, especially in terms of indirect costs, such as social support.[3,12,14] In the US, the economic burden of schizophrenia was estimated at $155.7 billion in 2013 ($134.4 billion–$174.3 billion based on sensitivity analyses) and included excess direct health care costs of $37.7 billion (24%), direct non-health care costs of $9.3 billion (6%) and indirect costs of $117.3 billion (76%).[15] In England, schizophrenia costs £11.8 billion per year, with around a third of this figure accounted for by direct expenditure on health and social care.[4]

Anatomic, neurotransmitter and immune system abnormalities have been implicated in the pathophysiology of schizophrenia. It seems that disruption of brain development is caused by genetic or environmental factors, or both.[6,16] Dysfunction of dopaminergic neurotransmission contributes to the genesis of positive symptoms, but other evidence highlights widespread and variable involvement of other brain areas and circuits. Disturbances of synaptic function might underlie abnormalities of neuronal connectivity, but the precise nature, location and timing of these events are uncertain.[17,18] The first clearly effective antipsychotic drugs, chlorpromazine and reserpine, were structurally different from each other, but they shared antidopaminergic properties. However, hypodopaminergic and hyperdopaminergic activities in the mesolimbic and mesocortical systems – leading, respectively, to negative and positive symptoms – may coexist. Moreover, newer antipsychotic drugs are able to block both dopamine D2 and serotonin (5HT) receptors. Clozapine is probably the most effective drug and is a particularly weak dopamine D2 antagonist. Thus, other neurotransmitters, such as norepinephrine, serotonin and gamma-aminobutyric acid (GABA), are involved. Some studies focused on the N-methyl-D-aspartate (NMDA) subclass of glutamate receptors, since its antagonism can lead to psychotic symptoms.[17–20] Some neuroimaging studies show differences in some areas between the brains of those with schizophrenia and those without the disease (eg, decrease of volume of temporal and hippocampus areas; abnormalities in neocortical and limbic regions).[21–23] Other, not mutually exclusive, theories include a deficit in myelin or white matter, association with cannabis use and genetic evidence of susceptibility genes.[24–27] Furthermore, immune function is disturbed in schizophrenia, which may result in overexpression of inflammatory cytokines and subsequent alteration of brain structure and function. Inflammation might be related to both psychopathology and other disturbances in patients with schizophrenia, since insulin resistance and metabolic alterations are common in these patients.[20,28,29] Schizophrenia is also correlated with poor physical health, including higher rates of obesity, diabetes, hypertension and cardiovascular disease.[16,30]

At present, treatment of schizophrenia mainly consists of a combination of medical, psychological and psychosocial strategies; however, a pressing need for more effective treatments and delivery of services still exists.[4,7] Antipsychotic medications, also known as neuroleptics or major tranquilizers, reduce the positive symptoms of schizophrenia and prevent relapses. Conventional or first-generation antipsychotics (FGAs) are primarily D2 blockers (eg, haloperidol and chlorpromazine) and have long been used to treat positive symptoms. However, they are usually associated with several adverse events, such as higher rates of extrapyramidal symptoms (EPS), namely, dystonia, parkinsonism, akathisia, sedation and anticholinergic side effects. Atypical or second-generation antipsychotics (SGAs) bind primarily, to different degrees, to both the D2 receptor and the 5HT2A receptor and may act at other receptors.[5,9,10,31] A range of SGAs, including risperidone, olanzapine, aripiprazole, quetiapine and ziprasidone, are available worldwide.[32–35]

Efficacy for negative, depressive and cognitive symptoms appears to be determined by the extent to which the drug may improve these other domains or exacerbate EPS and anticholinergic effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects.[34,36] Although SGAs have generally been believed to be associated with a lower risk of EPS but a higher risk of metabolic adverse effects (eg, weight gain), the substantial variation in these and other side effects among agents within both classes indicates that it is not clinically useful to make a categorical distinction between FGAs and SGAs. Both classes of drugs can lead to hyperprolactinemia, orthostatic hypotension, gastrointestinal distress and blood dyscrasias. Thus, choice of antipsychotic medication should be based on individual preference, prior treatment response, risk factors and adherence history.[34,36–38] Furthermore, the control of the disease is often incomplete, and some 20–30% of patients are considered refractory (not responsive to at least two different treatments). Despite

decades of effort, clozapine remains the most effective agent in otherwise non-responsive patients.[6,35]

Novel drugs are constantly introduced to provide better treatments. Iloperidone has been accepted on the market after 12 years of premarketing evaluation and was approved by the US Food and Drug Administration (FDA) in May 2009, becoming available for use in early 2010. Recently (2013), the European Medicines Agency (EMA) has accepted evaluation of this drug application.[30,37,39]

This drug is a piperidinylbenzisoxazole derivative, a tertiary amine whose primary mechanism of action is within the subtypes of combined D2/5HT2A antagonism, with greater affinity for the serotonin receptor (Ki value 5.6 nM), as well as for dopamines D2 and D3 (Ki values 6.3 and 7.1 nM, respectively) and noradrenergic A1 receptors (Ki value 0.36 nM). Iloperidone has low affinity for serotonin 5HT1A, dopamine D1 and histamine H1 receptors (Ki values 168, 216 and 437 nM, respectively) and no appreciable affinity (Ki value >1,000 nM) for cholinergic muscarinic receptors.[39–41] This pharmacodynamic profile with low affinity to H1 and M1 receptors would lead to minimal sedation, cognitive impairment and mild weight gain. The extremely low binding at cholinergic receptors suggests a low risk of anticholinergic symptoms (eg, blurred vision and dry mouth), as well as a lower EPS liability.[42,43]

Pharmacokinetic studies have determined that iloperidone, formulated as solid tablets, is well absorbed orally, with a bioavailability of 96%, and is extensively metabolized in the liver via CYP2D6 and CYP3A4. Peak serum iloperidone values were seen within 2–4 hours of administration. Iloperidone has a half-life of 13.5–14 hours and reaches a steady-state concentration within 3–4 days of initial administration. Initial dose is usually of 1 mg orally twice a day, with a target dose ranging between 6 and 12 mg twice a day and maximum dose of 24 mg/day.[35,39]

Clinical evidence

After performing our systematic search, 631 records were retrieved and 511 were screened by title and abstract reading. A total of 40 records were considered for full-text appraisal, and, of these, 18 studies were suitable for final analysis: eleven RCTs (two of them being long-term trials) and seven observational studies (case reports and case series) (Figure 1). The main characteristics of the studies are provided in Tables 1 and 2. All studies involved patients diagnosed with schizophrenia or related disorder or psychosis and were mainly conducted in USA (n=10), followed by India (n=7). Studies have compared the use of iloperidone (doses rang-ing from 2 to 24 mg/day) with placebo and/or active drugs (haloperidol, risperidone or ziprasidone). Overall, RCTs were well designed and properly reported randomization and/or blinding and patient dropouts (mean Jadad score of 3.2). Some records were grouped during the report, since they reported data from the same RCTs. All RCTs were sponsored by pharmaceutical industries (Vanda; Novartis) and properly declared conflicts of interest.

Efficacy measures

The measurement of the efficacy of drugs in clinical trials is usually carried out with psychometric scales. The Positive and Negative Syndrome Scale (PANSS) is commonly used to assess the severity of illness in patients with schizophrenia. There are 30 items in total, which are rated 1–7 (with 7 being most severe). The PANSS is identified by subscales: PANSS-T is used to identify the total score, while PANSS-P is for positive symptom score, PANSS-N (negative symptoms) and PANSS-GP (general psychopathology score), which includes items not considered in the positive or negative symptoms scales. The Brief Psychiatric Rating Scale (BPRS) is another rating scale used to assess the severity of illness in schizophrenia. The BPRS is derived from the PANSS and consists of 18 items. Finally, the Clinical Global Impressions (CGI) is a 7-point Likert scale commonly used in psychiatric studies to assess overall patient functioning. Specific subscales used are the CGI-S (severity) and CGI-C or CGI-I (change or improvement). The higher the score, the worse the severity of the disease.[44–46]

Short-term studies on iloperidone efficacy

We identified six Phase III trials that assessed the acute efficacy of iloperidone for schizophrenia, as well as two more long-term trials (Table 1).

Cutler et al[47–50] randomized 593 patients with schizophrenia (adults with mean age of 40±10.3 years) in a 2:1:1 fashion under double-blind conditions to iloperidone (24 mg/day), ziprasidone (160 mg/day) or placebo. Iloperidone was dosed twice daily (1, 2, 4, 6, 8, 10 and 12 mg) over days 1–7. Ziprasidone was chosen as the active comparator because its adverse effect profile and titration schedule are similar to iloperidone. The evaluated outcomes were changes in the measured scales, PANSS-T and subscales, as well as in CGI-S and BPRS scores during 4 weeks (1 week of drugs titration and 3 weeks of fixed-dose treatment). Improvement from baseline in PANSS-T was observed in patients treated with iloperidone (−12.0 points, $P<0.01$ versus placebo), as

Table 1 Characteristics of included RCTs and extension trials

Study	Treatment	N	Study design	Location	Age (years)	% Males
RCT Cutler et al[47] Lavedan et al[48] Thompson et al[49] Volpi et al[50]	• Iloperidone 12 mg 2×/day • Ziprasidone 80 mg 2×/day • Placebo	593	Prospective, multicenter, randomized, Phase III, double-blind, placebo- and ziprasidone-controlled trial	USA, India	40±10.3	79.6
RCT Potkin et al[51] (1)	• Iloperidone 4 mg/day • Iloperidone 8 mg/day • Iloperidone 12 mg/day • Haloperidol 15 mg/day • Placebo	621	Multicenter, randomized, double-blind, placebo-controlled trials	USA	38–40	71.2
RCT Potkin et al[51] (2)	• Iloperidone 4–8 mg/day • Iloperidone 10–16 mg/day • Risperidone 4–8 mg/day • Placebo	616			38–40	70.5
RCT Potkin et al[51] (3)	• Iloperidone 12–16 mg/day • Iloperidone 20–24 mg/day • Risperidone 6–8 mg/day • Placebo	706			37–40	62.0
RCT Citrome et al[55] Weiden et al[56]	• Iloperidone 12–24 mg/day gradual switch • Iloperidone 12–24 mg/day immediate switch Initial therapies were risperidone or olanzapine or aripiprazol	500	12-week, open-label, randomized trial	USA	43.3±11.0	67.0
RCT Potkin et al[53]	• Iloperidone 8 mg 2×/day • Iloperidone 12 mg 2×/day • Iloperidone 24 mg/day • Ziprasidone 80 mg 2×/day • Quetiapine 375 mg 2×/day	158	12-week, open-label, randomized trial	USA	18–65	Not reported
RCT Weiden et al[54]	• Iloperidone 4–12 mg 2×/day • Placebo	303	REPRIEVE study; randomized, double-blind placebo-controlled trial	USA, India, Ukraine	38.3±11.2	58.7
Extension trial Cutler et al[57]	• Iloperidone 12 mg/day • Iloperidone 24 mg/day • Placebo	173	25-week, open-label extension trial	USA, India	39.9±10.3	76.3
Extension trial Kane et al[58]	• Iloperidone 12 mg/day • Haloperidol 12 mg/day	489	Prospective, randomized, multicenter, open-label flexible-dose, extension phase	>3 countries	39.9±10.7	62.3

Note: *P values <0.05 versus comparators.
Abbreviation: RCT, randomized controlled trial; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions-severity; PANSS, Positive and Negative Syndrome Scale; T, total; P, positive; N, negative; GP, general psychopathology; EPS, extrapyramidal symptoms; ECG, electrocardiogram; REPRIEVE, A Randomized Trial of Iloperidone for Prevention of Relapse in Schizophrenia.

well as ziprasidone (−12.3 points, $P<0.05$ versus placebo). Moreover, iloperidone demonstrated significant improvement compared to placebo on the BPRS ($P<0.05$), PANSS-P ($P<0.001$), PANSS-N ($P<0.05$) and CGI-S ($P<0.01$).

Potkin et al[51] reported the results from three 6-week, double-blind, active- and placebo-controlled studies in patients with schizophrenia or schizoaffective disorder (aged 37–40 years). In the first trial, 621 patients were randomized to iloperidone (4, 8 or 12 mg/day), haloperidol (15 mg/day) or placebo. The primary outcome measure was change from baseline in the PANSS-T score, where improvement was observed in the iloperidone 12 mg/day group compared to pla-

Iloperidone main outcomes	Iloperidone incidence of adverse events	Conclusion
BPRS*, CGI-S*, PANSS-T*, PANSS-P*, PANSS-N*, PANSS-GP, drug discontinuation (35% being 16% adverse event-related)	Dizziness (17%), sedation (13%), weight increased (11%), tachycardia (9%), dry mouth (9%), nasal congestion (8%), heart rate increased (8%), hypotension (7%), somnolence (4%), agitation and anxiety (3%), EPS (3%)	Similar amount of adverse events and relevant changes on disease scales were observed with both active treatments. Iloperidone was effective, safe and well tolerated in schizophrenic patients with acute exacerbation.
Combined analyses: BPRS*, CGI-S*, PANSS-T*, PANSS-P*, PANSS-N*, PANSS-GP*, drug discontinuation, (1) 60.7%, (2) 48.0%, (3) 44.5%	Not evaluated	At least one iloperidone dosing group in each study demonstrated significantly better efficacy than placebo. Comparable efficacy score reductions were observed mainly for iloperidone 20–24 mg/day versus those receiving haloperidol or risperidone. These trials indicate that iloperidone is effective in schizophrenia.
CGI response rates: gradual switch: 17.5% (week 2), gradual switch: 81.2% (week 12), immediate switch: 26.1% (week 2), immediate switch: 84.4% (week 12)	Reported as: gradual switch and immediate switch, respectively, dizziness (8.8% and 14.2%), dry mouth (9.2% and 13.1%), fatigue (4.2% and 2.7%), insomnia (3.3% and 6.5%), nasal congestion (4% and 2%), nausea (4.2% and 4.2%), palpitations (1.3% and 3.8%), sedation (3.8% and 3.8%), somnolence (5.8% and 4.6%), weight increase (3% and 2%)	Switching to iloperidone can be accomplished either with a gradual crossover or immediate discontinuation of the prior antipsychotic; however, the immediate-switch method is associated with greater proportion of initial dizziness.
Assessment of heart rate-corrected QT interval, drug discontinuation related to adverse events: 3%	ECG abnormalities (21%), akathisia (8%), EPS (8%), psychosis (2%)	No patients experienced QTc changes of clinical concern (>Q500 ms). The only cardiovascular adverse events with iloperidone were non-concentration-dependent tachycardia that was mild in most patients and did not lead to further sequelae.
Relapse rate: 17.9%, time to relapse: 139 days, PANSS-T*, drug discontinuation (50.3% being 3.2% adverse event-related)	Dizziness (11.6%), somnolence (8.3%), dry mouth (6.8%), headache (6.4%), insomnia (5.6%), weight increase (5.4%), nausea (5.1%), schizophrenia (2.4%)	Flexible dosing of iloperidone with a modal dose of 12 mg/day was effective in preventing relapse in subjects previously stabilized on iloperidone. The adverse event profile showed low EPS.
PANSS-T and CGI-S: no signal of worsening, laboratory parameters (glycemia, lipids): normal values, drug discontinuation (56.9% being 24.4% adverse event-related)	Headache (13.9%), weight increase (9.2%), dizziness (6.9%), nausea (6.4%), sedation (6.4%), insomnia (5.2%), nasopharyngitis (4.6%), dry mouth (4.0%), somnolence (3.5%), psychotic disorder (3.5%), retrograde ejaculation (1.7%), suicidal (0.6%)	This study further supports the long-term safety and tolerability of iloperidone for schizophrenia, including its favorable effect on metabolic laboratory parameters and low propensity to cause akathisia or EPS.
PANSS, CGI-S, BPRS: no signal of worsening, laboratory parameters (glycemia, lipids): normal values, drug discontinuation (36.4% being 3.8% adverse event-related)	Insomnia (21.1%), headache (8.6%), anxiety (8.1%), agitation (6.7%), dizziness (5.8%), akathisia (3.5%), tremor (3.3%), bradykinesia (1.3%), dystonia (1.1%), EPS (0.6%), death (0.5%)	Iloperidone is equivalent to haloperidol in time to relapse and presented a better profile in the EPS Rating Scale scores. The long-term efficacy and favorable safety profile of iloperidone make this drug a suitable option for maintenance therapy.

cebo (−9.9 versus −4.6 points; $P<0.047$) and for haloperidol versus placebo (−13.9 versus −4.6 points; $P<0.001$). Moreover, significant improvement in the iloperidone 12 mg/day group was noted in the BPRS scale ($P<0.042$ against placebo).

In the second trial, 616 patients were randomized to iloperidone (4–8 mg/day), iloperidone (10–16 mg/day), ris-peridone (4–8 mg/day) or placebo. Significant improvement from baseline on the primary outcome total BPRS score was seen in the iloperidone 4–8 mg/day group ($P<0.012$ versus placebo), 10–16 mg/day group ($P<0.001$ versus placebo) group and the risperidone group ($P<0.001$ versus placebo). Furthermore, statistically significant improvement on the

Table 2 Characteristics of included observational studies

Study	Treatment	N	Study design	Location	Age (years)	Gender	Adverse events	Iloperidone related	Conclusion
Achalia and Andrade[59]	Iloperidone 8–16 mg/day	1	Case report	India	29	Male	VPCs	Probably	Clinically significant and symptomatically distressing; diagnosed as VPC. It may be an uncommon adverse effect of iloperidone, possibly mediated by iloperidone-induced alpha 2c adrenoceptor blockade.
Das et al[70]	Iloperidone 6–12 mg 2×/day	57	Case series	India	17–39	Not reported	23 patients nasal congestion, 8 hypotension, 10 fatigue and dizziness, 4 dry mouth, 4 weight gain, 3 tachycardia, 2 mild hypoglycemia	Probably	Adverse events were experienced after taking iloperidone for at least 4 weeks. Nasal congestion was the most extensive and frequent complaint in this specific population.
Dutta et al[60]	Iloperidone 8 mg/day	1	Case report	India	35	Female	Galactorrhea	Yes	Iloperidone can cause hyperprolactinemic galactorrhea even at low dosage and after a considerable period into the treatment.
Freeman et al[71]	Iloperidone 8 mg 2×/day	2	Case series	USA	22, 21	Males	Retrograde ejaculation	Yes	Clinicians should be aware of the potential for newer antipsychotics with strong alpha 1 blockade such as iloperidone to cause retrograde ejaculation as an adverse event.
Muzyk et al[72]	Iloperidone 1–4 mg 2×/day	1	Case report	USA	24	Male	Angioedema	Yes (iloperidone and haloperidol association)	This case revealed a potential interaction of drugs (iloperidone and haloperidol) and highlighted the risk of cross-sensitivity between different antipsychotics in the cardiovascular system.
Ravani et al[73]	Iloperidone 1–8 mg/day	5	Case series	India	31, 29, 19, 30, 32	Males	Ejaculatory dysfunction	Yes	The ejaculatory dysfunctions following treatment with iloperidone could be due to the blocking of alpha 1 adrenergic receptor.
Rodriguez et al[74]	Iloperidone 6 mg/day	1	Case report	USA	42	Male	Priapism	Yes	This case highlights important risk factors that should be considered when using iloperidone given it is a potent blocker of the alpha adrenergic receptor action.

Abbreviation: VPC, ventricular premature contraction.

PANSS-P and PANSS-GP subscales and CGI-S score was observed for iloperidone in different doses.

In the third study, researchers randomized 706 patients to iloperidone (12–16 mg/day), iloperidone (20–24 mg/day), risperidone (6–8 mg/day) or placebo. Compared with placebo, the iloperidone 20–24 mg/day ($P<0.010$) and risperidone groups ($P<0.001$) demonstrated statistically significant improvement in the primary outcome (BPRS changes from baseline). The iloperidone 20–24 mg/day group also resulted in significant reductions in PANSS-T,

PANSS-P, PANSS-N and CGI-S scores compared with placebo. Lower doses of iloperidone (12–16 mg/day group) did not result in a significant improvement in the BPRS, although they did lead to significant improvement on the CGI-S (*P*<0.028). Citrome et al[52] conducted a post hoc analysis of all four abovementioned RCTs (n=2,401), using an intention-to-treat analysis, and showed that iloperidone (10–16 and 20–24 mg/day) was associated with significant improvements on all mentioned scales compared with placebo.

Furthermore, three other RCTs were recently published.[53–56] Potkin et al[53] have investigated the impact of iloperidone (8, 12 and 24 mg/day) in 158 patients (18–65 years), compared to ziprasidone or quetiapine in heart rate-corrected QT interval. The results showed no clinically concerning changes in all evaluated groups, and the adverse events reported in the iloperidone group were mild and did not lead to further sequelae.

The REPRIEVE study (A Randomized Trial of Iloperidone for Prevention of Relapse in Schizophrenia), conducted by Weiden et al,[54] randomized 303 patients to iloperidone (4–12 mg, twice daily) or placebo for 24 weeks. Apart from changes in psychometric scales, such as PANSS-T, where iloperidone showed significant improvements compared to placebo (*P*<0.05), the authors assessed the mean time to relapse. Results showed a mean of 71 days for placebo and 139 days for iloperidone (*P*<0.0001). Flexible dosing of iloperidone for maintenance-phase therapy (modal dose: 12 mg/day) was effective in preventing relapse in subjects previously stabilized on iloperidone.

Finally, the study of Weiden et al[56] and Citrome et al[55] was a 12-week, open-label trial with 500 patients (43.3±11.0 years), which evaluated the gradual- or immediate-switch strategies from risperidone, olanzapine or aripiprazole to iloperidone of patients experiencing inadequate efficacy and/or poor tolerability. Patients were randomized to switch to iloperidone, either gradually (down-titration of current therapy over the first 2 weeks to 50% on day 1; 25% by week 1; 0% by week 2) or immediately. All patients were titrated on iloperidone to 6 mg twice daily by day 4, then, flexibly dosing between 6 and 12 mg twice daily, as needed. The primary outcome was CGI improvement at week 12. Response rates were similar between groups during study periods and confirmed the clinical improvement in both groups without any significant difference in ratings of overall efficacy. However, the immediate-switch method was associated with a greater proportion of dizziness.

Long-term studies on iloperidone effectiveness

Considering the long-term extension trials[57,58] with >662 patients combined, iloperidone showed a good overall effectiveness profile despite dosing (12–24 mg/day) against placebo and haloperidol. No signs of worsening were observed in any rating scale (PANSS, CGI and BPRS). Laboratory parameters, such as glycemia, lipid profile (cholesterol, triglycerides, high-density lipoprotein [HDL] and low-density lipoprotein [LDL]), prolactin level and weight, did not change drastically during the study and values were, overall, within normal.

Therefore, published studies have demonstrated that iloperidone has acute and long-term efficacy for schizophrenia, especially when compared to placebo, and can be considered similar to other active drugs such as risperidone, haloperidol and ziprasidone.

Safety and tolerability

Almost all included RCTs reported data on safety and tolerability profiles of iloperidone (Table 1). Observational studies (Table 2) were gathered to contribute as evidence for clinical practice.

The most commonly reported adverse events (reported by >5% of patients in the studies) were dizziness (especially when switching from another antipsychotic to iloperidone without gradual titration), sedation, weight gain, dry mouth, nasal congestion, hypotension, headache, nausea, sleep disorders (insomnia, somnolence) and heart-related changes (tachycardia, palpitations and electrocardiogram [ECG] alterations). EPS was reported in three trials, with rates ranging from 0.6% to 8%. Compared to other drugs, haloperidol showed a higher propensity to cause EPS, tremor, akathisia and dystonia. Risperidone was also more associated with EPS, tremor and somnolence than iloperidone.

As expected, owing to the mechanism of action of iloperidone, this drug has a more favorable EPS and akathisia profile than other D2/5HT2A antagonists. The adverse events profile of iloperidone appears to be a cross between that of ziprasidone and risperidone. Compared with ziprasidone, iloperidone caused similar QTc interval prolongation[53] but with greater potential for weight gain, which should be taken into account when considering patients individual characteristics. Rates from 4% to 13% were found for iloperidone causing sedation, which is also an important concern for patients and should be considered during therapeutic decision-making. Although no cases of iloperidone-associated sudden death due to arrhythmias have been reported, avoidance of this drug may be prudent for patients who are medically susceptible to

heart diseases or for patients taking concomitant medications that lengthen the QT interval. These precautions are similar to those for ziprasidone.[39,40,59] So far, only one case of ventricular premature contractions has been published and is possibly related to iloperidone inducing alpha 2c receptor blockage.[59]

Furthermore, risperidone is noted to have the highest propensity of all SGA agents to cause hyperprolactinemia, with potential to cause oligomenorrhea or amenorrhea in women and erectile dysfunction in men. These adverse events were considered uncommon reactions to iloperidone. Two observational studies referred to ejaculatory dysfunction, reported in men from 20 to 30 years old, which was also reported in an extension trial[57] in ~2% of the patients and appears to be due to the blocking of alpha 1 adrenergic receptors. Moreover, one case of galactorrhea was reported but is considered rare.[60] However, iloperidone causes significantly more orthostatic hypotension than risperidone, and this may be a concern for some patients and requires the use of divided doses and gradual dosage increases (titration).[40] Some other mild events, such as nasal congestion, dry mouth and sleep disorders, seem to stabilize over time, as observed in the extension trials, and can be well managed.

It is worth noting that there is a potential interaction of the drugs iloperidone and haloperidol, leading to angioedema, which highlights the risk of cross-sensitivity of antipsychotics to cause cardiovascular problems. Concomitant medications must be closely monitored; the dose of iloperidone needs to be reduced in the presence of other drugs, especially drugs that are strong CYP450 inhibitors.[53,59,61] So far, no evidence on iloperidone causing acute kidney injury (AKI) is available. Since other atypical antipsychotics (quetiapine, risperidone and olanzapine) are linked to increased risk of hospitalization for AKI in elderly patients, caution for the use of iloperidone in elderly is recommended.[62]

Considering the tolerability profile of iloperidone, discontinuation rates ranged from 3% to almost 61%. These differences may be due to the size of the studies, population characteristics and follow-up trials. Rates were similar to placebo and active comparators in all clinical trials ($P>0.05$) and were more related, in order, to consent withdrawal, unsatisfactory therapeutic response and adverse events. In the trial published by Cutler et al,[47] ~16% of patients discontinued due to adverse events. Other causes of treatment dropout were consent withdrawal (58%) and inefficacy (21%). In the study of Potkin et al,[51] iloperidone was discontinued by ~25% of patients in each group due to unsatisfactory effect and by ~7% due to adverse events. In long-term trials, Cutler et al[57] showed that less than half of the patients (41.6%) completed the extension phase: 25 patients discontinued

owing to adverse events, 36 withdrew consent, eleven had unsatisfactory therapeutic response and 18 were lost during follow-up. In the study of Kane et al[58], discontinuation rates owing to adverse events of iloperidone were inferior to those from haloperidol (3.8% and 7.6%, respectively). However, more patients from iloperidone withdrew consent (14.5% iloperidone and 8.5% haloperidol) and a similar number discontinued due to therapeutic failure (~10%).[57,58]

Overall, iloperidone was considered reasonably tolerable and to have a promising safety profile among adult patients, and no further serious events were reported. No safety data are so far available for children and adolescents.[42] Other previous studies, systematic reviews and meta-analyses showed that iloperidone is an acceptable drug, even when compared to placebo or other antipsychotics, especially in terms of modest weight gain, no medically important changes in lipid and glucose levels and little in the way of prolactin elevation and EPS.[31,39,52,63]

Pricing

Schizophrenia therapeutics yield $6.3 billion in market sales per year around the world, and this will grow to $7.9 billion by 2022.[64] Currently, there is no formal pharmacoeconomic study on the cost-effectiveness of iloperidone for treating schizophrenia. An estimated monthly acquisition cost comparison among usual maintenance doses of atypical antipsychotics showed that the cost of iloperidone of $630 is $50 more than that of asenapine, $200 more than that of ziprasidone and $400 more than the cost of generic risperidone.[30,40] Thus, when referring only to acquisition costs of iloperidone, the higher price can hamper its use in clinical practice. However, it is important to compare the impact of iloperidone with other antipsychotics in reducing adverse events, hospitalization and ineffectivity. Thus, pharmacoeconomic studies should be performed.

Place in therapy

Atypical antipsychotics are now recommended as first-line agents for the treatment of patients with schizophrenia. Con-

Table 3 Iloperidone clinical profile

Advantages	Disadvantages
Low propensity to cause EPS	Requires slow titration to therapeutic doses, which may delay onset of therapeutic effect
Low propensity to cause prolactin increase	Risk of orthostatic hypotension, sedation and dizziness
Low propensity to change lipid and glycemic profile	Not indicated for patients with any risk for clinical QTc prolongation
No dose adjustment required on basis of renal functioning	Potential interactions with agents that inhibit or induce CYP2D6 and CYP3A4

Abbreviation: EPS, extrapyramidal symptoms.

sidering all exposed, iloperidone has favorable properties that may promote and spread its use. Table 3 shows a summary of the advantages and disadvantages of this drug.

Iloperidone is clearly more effective than placebo at dosages exceeding 8 mg daily, with increasing efficacy noted at dosages of up to 20–24 mg daily, given in equally divided doses. Furthermore, this drug appears to be as effective as haloperidol, risperidone and ziprasidone when it comes to improving results in validated psychometric scales of schizophrenia symptoms.

Iloperidone seems an attractive choice, particularly for patients whose compliance is limited by side effects that occur more frequently with other antipsychotics. Further systematic reviews and meta-analyses have also shown that iloperidone did not significantly cause EPS and akathisia, increased prolactin or changed laboratory parameters when compared to placebo and other antipsychotics.

Poor or non-adherence behavior is common in psychiatry (rates >50%) and attributed to lack of efficacy, poor tolerability and patient's denial of the disease (in approximately one-third to one-half of diagnosed patients).[65,66] For all-cause discontinuation, iloperidone shows a tolerable profile compared to haloperidol, lurasidone, sertindole and ziprasidone,[31,63] and despite producing some significant weight gain, this drug seems to be well accepted among patients. However, the slow titration schedule, adapted to reduce dizziness, sedation and orthostatic hypotension, may limit the use of this agent in an acute setting. The usual target effective range is 12–24 mg daily, given in two divided doses. The maximum labeled dose of iloperidone is 12 mg twice daily. Furthermore, given the capacity of iloperidone to extend QTc interval on ECG, it is not recommended for use in patients with heart-related diseases or in coadministration with other QT-prolonging drugs.[31,63,67,68] In this context, long-acting injectable formulations (LAIs) have been identified as a means of improving adherence, reducing dose-related side-effects due to lower peak of drug plasma levels and helping to prevent relapse. Currently, LAIs of fluphenazine, haloperidol, olanzapine, risperidone, aripiprazole and paliperidone are available for use. The iloperidone crystalline LAI is still under investigation in Phase II and III trials with a dosing interval of 28 days.[65,66,69]

Therefore, available evidence suggests that iloperidone may be classified as having low health-related risks and should be incorporated into clinical practice with few contraindications. However, drug acquisition costs certainly limit its use. Further reasonable pharmacoeconomic studies, resource utilization and pricing should be reconsidered to provide more accessible therapeutic options to treat schizophrenia. Schizophrenia is considered one of the worst mental disorders worldwide, with a very disabling prognosis. Continuing to provide novel treatment options may help patients to overcome some limits and experience recovery and independence. Other studies evaluating patients' outcomes of quality of life, general functioning and satisfaction with treatment would also help to define the place of iloperidone in therapy.

Author contributions

RP and FFL designed the study and wrote the protocol. FST and AW screened and abstracted publications. FST, AW, FFL and RP analyzed data and wrote the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors reviewed the manuscript for accuracy and scientific content.

Disclosure

The authors report no conflicts of interest in this work.

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