Iloperidone - New Second Generation Antipsychotic: Pharmacological Aspects and Schizophrenia Clinical Management

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Review Article

Abstract

Iloperidone is a new atypical antipsychotic drug approved by FDA for the treatment of schizophrenia. In this article, we searched the published randomized controlled trials (RCT) and other literature to review the efficacy and safety of iloperidone using the following database (Science Direct, PubMed) and illustrate its role in the management of schizophrenia. Iloperidone showed efficacy by causing significant improvements in psychiatric scales such as Positive and Negative Syndrome scale (PANSS) and clinical global impressions (CGI). Iloperidone was associated with a number of common side effects such as metabolic and cardiovascular side effects. This review illustrated that iloperidone was well tolerated with significant improvements in disease severity and symptom intensity control in patients suffering with schizophrenia, however, iloperidone was associated with a significantly higher risk of metabolic and cardiovascular side effects with minimal extrapyramidal side effects. These findings would guide psychiatrists and pharmacists in their clinical role for supporting the care of psychiatric patients.

Keywords: Iloperidone, atypical antipsychotic, schizophrenia, psychiatrists, pharmacists, side effects.

Introduction

Schizophrenia is a chronic and debilitating psychiatric disorder with significant morbidity and mortality (1) with a substantial impact on the patients and their carers' psychological, physical and social life (2). Despite the available management options, several patients suffer from treatment-resistant or poor prognosis (3). Schizophrenia prevalence is 0.5%-1% worldwide (4) with the associated management challenges such as frequent antipsychotics switching and poor compliance (5). Atypical antipsychotics are the main group of pharmacological treatments used in the management of schizophrenia due to their favourable side effects (SE) profile compared to the typical antipsychotics (6).

Iloperidone, a new second generation antipsychotics (SGA) with similar structure to risperidone (7), is used for the management of schizophrenia and other psychotic disorders (8). The recommended iloperidone daily dose is 12-24 mg divided as 2 doses (9) with recommended dose titration - starting dosage of 1 mg twice daily to minimize postural hypotension and target dose of 6 mg bid achieved in 4 – 7 days (10,11).

Iloperidone: Pharmacodynamics and pharmacokinetics

Iloperidone has strong affinity for noradrenaline, dopamine, and serotonin receptors. At clinical doses, iloperidone blocks 5-HT2A receptors and reduces dopamine D2 receptor-mediated neurotransmission (12). Iloperidone also binds to D3, alpha2C, 5-HT1A, and 5-HT6 receptors (13). 5-HT1A stimulation and 5-HT6 antagonism are of primary importance for iloperidone possible beneficial effects on cognition (12). Iloperidone strong 5-HT2A antagonism could stimulate histamine neuron activity with pro-cognitive properties (14). Research using computer models suggested that the clinical effects of iloperidone occur through dopamine receptor coupling in cortical neurons (15).

Iloperidone also affects the noradrenergic system (alpha2C antagonism) resulting in cognitive symptoms changes as iloperidone, when compared with other antipsychotics, has the highest alpha2C/alpha2A ratio (16). Iloperidone also increased dopamine and acetylcholine release in the medial prefrontal cortex via actions on 5-HT1A (17), increased dopa accumulation in response to D2 receptor antagonism with clozapine-like effects (18) and decreased 5-HT2 receptors (19). Administered orally, iloperidone is well absorbed with 96% bioavailability (20), highly bound to plasma proteins (21). Peak serum concentration is achieved within 2 - 3 hours and eliminated slowly ($t_{1/2}$ 14 hours) (22). Iloperidone was extensively metabolized with CYP1A2, CYP2E1, CYP2D6 and CYP3A4 enzymes (23). When prescribing iloperidone, CYP2D6 extensive and poor metabolizers need to be checked (24) due to different plasma concentrations of iloperidone and its metabolites (25); for example, elimination half-life was 18 h for extensive CYP2D6 metabolizers and around 33 h for poor CYP2D6 metabolizers (26). Iloperidone major metabolite has receptor affinity profile similar to iloperidone and likely to contribute to its clinical effects (27). Iloperidone quality, safety and efficacy could also be affected by acidic, basic hydrolysis and oxidative degradation (8).

Iloperidone efficacy in human studies

Iloperidone showed efficacy in relapse prevention in schizophrenia (relapse rates was just 20% compared to around 63% for placebo) with longer mean time to relapse (139 days versus 71 days) (28). In a big clinical trial with 500 patients on risperidone, olanzapine, or aripiprazole switched to iloperidone, improvement in Clinical Global Impression (CGI) scale was observed (29,30). Iloperidone was also associated with improved Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale-total (PANSS-T) score, and PANSS-positive and

PANSS-negative scores (31). Further two trials confirmed iloperidone beneficial decrease of PANSS-T (11,32).

Iloperidone ameliorated excitement/hostility; depression/anxiety; cognition; positive and negative scales (33) and was successful in improving mania and depression scores in mixed mood states, considered difficult to manage in bipolar disorders (34). As iloperidone has the highest affinity to alpha-1 compared to other antipsychotics, it could be helpful in posttraumatic stress disorder management like prazosin (alpha-1 antagonist) with its D2 and 5-HT2 antagonist activities reducing hypervigilance (35).

Iloperidone efficacy in animal studies

Cognitive functions are normally impaired in schizophrenia, while iloperidone showed efficacy in improving choice accuracy (36) and cognitive dysfunction in rat models (37). In experiments using apomorphine and phencyclidine, pre-treatment with iloperidone demonstrated beneficial behavioural actions (38). Iloperidone increased social interaction (39) with its weak D2 and potent alpha-2 antagonism helping to reduce alcohol drinking issues (40).

Safety and tolerability of Iloperidone

Iloperidone most common side effects (SE) were dizziness (5.1%-23.2%), somnolence (4%-13%), dyspepsia (4.8%-7.8%), insomnia (18.1%), anxiety (10.8%) and dry mouth (5.2%-10.4%) with low rates of extrapyramidal disorder (2.5%) or akathisia (3.7 %) (11,28,41). A dose relationship for dizziness, somnolence and dry mouth existed; e.g. number to harm (NNH) for somnolence was 25 for iloperidone 10-16 mg/day and 10 for 20-24 mg/day (42). Nasal congestion, fatigue, sedation and tachycardia occurred especially with higher doses (31). Long-term management with high doses caused SE such as headache (13.9%), weight increase (9.2%), dizziness (6.9%), nausea (6.4%), sedation (6.4%) and insomnia (5.2%) (43). Iloperidone was

also associated with a moderate risk of metabolic syndrome or cardiovascular events (44). Statistically significant changes in serum glucose found with ≥7% weight increase (NNH = 11) (45), with young or low baseline body mass index patients most vulnerable (44). Iloperidone prolongs QTc interval to a higher extent compared to quetiapine and co-administration of metabolic inhibitors could further increase risk of QTc changes especially in patients with CYP2D6 polymorphisms (46). Moreover, alpha 2c antagonism could lead to ventricular premature contractions (47) and predispose to cardiac arrhythmias and sudden death; no patient suffered from QT interval of 500 msec or greater (32). Iloperidone has a favourable prolactin profile compared to other antipsychotics, but is associated with disorders of ejaculation such as priapism due to its alpha1- antagonist properties (48-50).

Withdrawal of iloperidone could lead to increased heart rate/palpitations and urinary incontinence (34), hence gradual withdrawal/switching is recommended (29). Discontinuation with iloperidone due to SE was just 4.8% compared to 7.6% for haloperidol and 6.2% for risperidone (51). Caution is needed in elderly patients due to orthostatic SE (9). Iloperidone could increase the incidence of psychotic disorders during the postpartum period (52) with limited safety data for iloperidone in breast feeding (53). Reported rare SE include respiratory depression (54); angioedema (55), neuroleptic malignant syndrome (56) and Tardive Dyskinesia (57). Combinations with other psychiatric medications result in pharmacokinetic and pharmacodynamic interactions such as increase in QTc interval when fluoxetine or paroxetine co-administered with iloperidone (58). Iloperidone co-administered with fluoxetine resulted in significant weight gain (59), while its use while patients taking illicit drugs (e.g. cocaine) led to respiratory failure with mandated respiratory support and prolonged QTc (60).

Pharmacogenomics

Polymorphisms associated with iloperidone efficacy were identified within the neuronal PAS domain protein 3 gene (NPAS3) (61) with more than 75% of iloperidone-treated patients with the optimal genotype combinations showed at least 20% improvement compared with just 37% for patients with other genotypes (62).

Discussion

First generation antipsychotics have facilitated hospital discharge and community psychiatric treatment, while SGA lead to lower risk of extrapyramidal and cognitive SE with better quality of life (63). On the other hand, SGAs have been associated with metabolic SE such as weight gain, lipid/glycaemic imbalance, risk of diabetes mellitus and diabetic ketoacidosis (63). Iloperidone was shown to be effective like haloperidol, risperidone and ziprasidone in reducing schizophrenia symptoms and preventing relapses (66). Common SE of iloperidone were mild including dizziness, hypotension, dry mouth and orthostatic hypotension (70). Similar to paliperidone, quetiapine and risperidone; iloperidone could cause weight gain and glucose imbalance especially in young, drug-naïve patients with healthy lifestyle counselling recommended (67). Iloperidone could also cause QTc prolongation, with low risk of akathisia, extrapyramidal symptoms compared to haloperidol and risperidone (68). This low risk may be linked to its alpha1 and HT2A antagonism (69). Patients using other antipsychotic (e.g. risperidone) can easily switch to iloperidone with no serious impact on safety or efficacy (2).

Clinical judgment while taking scientific evidence and patients' preferences in consideration is of primary importance in schizophrenia management (65). Although iloperidone clinical trials were conducted, effectiveness studies as well as safety data in elderly, young and pregnant patients are still lacking (71), especially elderly, who suffer from high comorbidity rates (psychiatric and medical); age-related pharmacokinetics changes and polypharmacy risk (72).

References

(1) Sistik P, Turjap M, Iordache AM, Saldanha HM, Lemr K, Bednar P. Quantification of selected antidepressants and antipsychotics in clinical samples using chromatographic methods combined with mass spectrometry: A review (2006-2015). Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016 Mar;160(1):39-53.

(2) Tonin FS, Wiens A, Fernandez-Llimos F, Pontarolo R. Iloperidone in the treatment of schizophrenia: an evidence-based review of its place in therapy. Core Evid 2016 Dec 14;11:49-61.

(3) Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Asenapine, blonanserin, iloperidone, lurasidone, and sertindole: distinctive clinical characteristics of 5 novel atypical antipsychotics. Clin Neuropharmacol 2013 Nov-Dec;36(6):223-238.

(4) Rado JT, Janicak PG. Long-term efficacy and safety of iloperidone: an update. Neuropsychiatr Dis Treat 2014 Feb 26;10:409-415.

(5) Caccia S, Pasina L, Nobili A. New atypical antipsychotics for schizophrenia: iloperidone. Drug Des Devel Ther 2010 Feb 18;4:33-48.

(6) Orsolini L, Tomasetti C, Valchera A, Vecchiotti R, Matarazzo I, Vellante F, et al. An update of safety of clinically used atypical antipsychotics. Expert Opin Drug Saf 2016 Oct;15(10):1329-1347.

(7) Uto Y. 1,2-Benzisoxazole compounds: a patent review (2009 - 2014). Expert Opin Ther Pat 2015 Jun;25(6):643-662.

(8) Pandeti S, Rout TK, Tadigoppula N, Thota JR. Identification of stress degradation products of iloperidone using liquid chromatography coupled with an Orbitrap mass spectrometer. Rapid Commun Mass Spectrom 2017 Aug 30;31(16):1324-1332.

(9) Marino J, Caballero J. Iloperidone for the treatment of schizophrenia. Ann Pharmacother 2010 May;44(5):863-870.

(10) Citrome L. Iloperidone: a clinical overview. J Clin Psychiatry 2011;72 Suppl 1:19-23.

(11) Crabtree BL, Montgomery J. Iloperidone for the management of adults with schizophrenia. Clin Ther 2011 Mar;33(3):330-345.

(12) Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol 2011 Feb;11(1):59-67.

(13) Kalkman HO, Feuerbach D, Lotscher E, Schoeffter P. Functional characterization of the novel antipsychotic iloperidone at human D2, D3, alpha 2C, 5-HT6, and 5-HT1A receptors. Life Sci 2003 Jul 18;73(9):1151-1159.

(14) Morisset S, Sahm UG, Traiffort E, Tardivel-Lacombe J, Arrang JM, Schwartz JC. Atypical neuroleptics enhance histamine turnover in brain via 5-Hydroxytryptamine2A receptor blockade. J Pharmacol Exp Ther 1999 Feb;288(2):590-596.

(15) Geerts H, Roberts P, Spiros A, Potkin S. Understanding responder neurobiology in schizophrenia using a quantitative systems pharmacology model: application to iloperidone. J Psychopharmacol 2015 Apr;29(4):372-382.

(16) Kalkman HO, Loetscher E. alpha2C-Adrenoceptor blockade by clozapine and other antipsychotic drugs. Eur J Pharmacol 2003 Feb 21;462(1-3):33-40.

(17) Ichikawa J, Li Z, Dai J, Meltzer HY. Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. Brain Res 2002 Nov 29;956(2):349-357.

(18) Szewczak MR, Corbett R, Rush DK, Wilmot CA, Conway PG, Strupczewski JT, et al. The pharmacological profile of iloperidone, a novel atypical antipsychotic agent. J Pharmacol Exp Ther 1995 Sep;274(3):1404-1413.

(19) Szczepanik AM, Brougham LR, Roehr JE, Conway PG, Ellis DB, Wilmot CA. Ex vivo studies with iloperidone (HP 873), a potential atypical antipsychotic with dopamine D2/5-hydroxytryptamine2 receptor antagonist activity. J Pharmacol Exp Ther 1996 Aug;278(2):913-920.

(20) Arif SA, Mitchell MM. Iloperidone: A new drug for the treatment of schizophrenia. Am J Health Syst Pharm 2011 Feb 15;68(4):301-308.

(21) Albers LJ, Musenga A, Raggi MA. Iloperidone: a new benzisoxazole atypical antipsychotic drug. Is it novel enough to impact the crowded atypical antipsychotic market? Expert Opin Investig Drugs 2008 Jan;17(1):61-75.

(22) Sainati SM, Hubbard JW, Chi E, Grasing K, Brecher MB. Safety, tolerability, and effect of food on the pharmacokinetics of iloperidone (HP 873), a potential atypical antipsychotic. J Clin Pharmacol 1995 Jul;35(7):713-720.

(23) Caccia S. New antipsychotic agents for schizophrenia: pharmacokinetics and metabolism update. Curr Opin Investig Drugs 2002 Jul;3(7):1073-1080.

(24) Brennan MD. Pharmacogenetics of second-generation antipsychotics. Pharmacogenomics 2014 Apr;15(6):869-884.

(25) Pei Q, Huang L, Huang J, Gu JK, Kuang Y, Zuo XC, et al. Influences of CYP2D6(*)10 polymorphisms on the pharmacokinetics of iloperidone and its metabolites in Chinese patients with schizophrenia: a population pharmacokinetic analysis. Acta Pharmacol Sin 2016 Nov;37(11):1499-1508.

(26) Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. Expert Opin Drug Metab Toxicol 2010 Dec;6(12):1551-1564.

(27) Subramanian N, Kalkman HO. Receptor profile of P88-8991 and P95-12113, metabolites of the novel antipsychotic iloperidone. Prog Neuropsychopharmacol Biol Psychiatry 2002 Apr;26(3):553-560.

(28) Weiden PJ, Manning R, Wolfgang CD, Ryan JM, Mancione L, Han G, et al. A Randomized Trial of Iloperidone for Prevention of Relapse in Schizophrenia: The REPRIEVE Study. CNS Drugs 2016 Aug;30(8):735-747.

(29) Citrome L, Weiden PJ, Alva G, Glick ID, Jackson R, Mattingly G, et al. Switching to iloperidone: An omnibus of clinically relevant observations from a 12-week, open-label, randomized clinical trial in 500 persons with schizophrenia. Clin Schizophr Relat Psychoses 2015 Jan;8(4):183-195.

(30) Weiden PJ, Citrome L, Alva G, Brams M, Glick ID, Jackson R, et al. A trial evaluating gradual- or immediate-switch strategies from risperidone, olanzapine, or aripiprazole to iloperidone in patients with schizophrenia. Schizophr Res 2014 Mar;153(1-3):160-168.

(31) Citrome L, Meng X, Hochfeld M, Stahl SM. 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 Jan;27(1):24-32.

(32) Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol 2008 Apr;28(2 Suppl 1):S20-8.

(33) Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. Schizophr Res 2011 Sep;131(1-3):75-81.

(34) Singh V, Arnold JG, Prihoda TJ, Martinez M, Bowden CL. An Open Trial of Iloperidone for Mixed Episodes in Bipolar Disorder. J Clin Psychopharmacol 2017 Oct;37(5):615-619.

(35) Shuman MD, Mcgrane IR. Rationale for iloperidone in the treatment of posttraumatic stress disorder. Innov Clin Neurosci 2014 May;11(5-6):23-25.

(36) Gemperle AY, McAllister KH, Olpe HR. Differential effects of iloperidone, clozapine, and haloperidol on working memory of rats in the delayed non-matching-to-position paradigm. Psychopharmacology (Berl) 2003 Sep;169(3-4):354-364.

(37) Mutlu A, Mutlu O, Ulak G, Akar F, Kaya H, Erden F, et al. Superior effects of quetiapine compared with aripiprazole and iloperidone on MK-801-induced olfactory memory impairment in female mice. Biomed Rep 2017 May;6(5):567-570.

(38) Barr AM, Powell SB, Markou A, Geyer MA. Iloperidone reduces sensorimotor gating deficits in pharmacological models, but not a developmental model, of disrupted prepulse inhibition in rats. Neuropharmacology 2006 Sep;51(3):457-465.

(39) Corbett R, Hartman H, Kerman LL, Woods AT, Strupczewski JT, Helsley GC, et al. Effects of atypical antipsychotic agents on social behavior in rodents. Pharmacol Biochem Behav 1993 May;45(1):9-17.

(40) Khokhar JY, Green AI. Effects of iloperidone, combined with desipramine, on alcohol drinking in the Syrian golden hamster. Neuropharmacology 2016 Jun;105:25-34.

(41) Kane JM, Lauriello J, Laska E, Di Marino M, Wolfgang CD. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol 2008 Apr;28(2 Suppl 1):S29-35.

(42) 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 Aug;63(8):1237-1248.

(43) Cutler AJ, Kalali AH, Mattingly GW, Kunovac J, Meng X. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. CNS Spectr 2013 Feb;18(1):43-54.

(44) Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert Opin Drug Saf 2015 Jan;14(1):73-96.

(45) De Hert M, Yu W, Detraux J, Sweers K, van Winkel R, Correll CU. 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 Sep 1;26(9):733-759.

(46) Potkin SG, Preskorn S, Hochfeld M, Meng X. 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 Feb;33(1):3-10.

(47) Achalia R, Andrade C. Ventricular premature contractions associated with iloperidone. Indian J Psychiatry 2013 Apr;55(2):195-196.

(48) Ravani NN, Katke PH. Iloperidone-induced ejaculatory dysfunction: A case series. Indian J Psychiatry 2016 Jan-Mar;58(1):87-89.

(49) Rodriguez-Cabezas LA, Kong BY, Agarwal G. Priapism associated with iloperidone: a case report. Gen Hosp Psychiatry 2014 Jul-Aug;36(4):451.e5-451.e6.

(50) Freeman SA. Iloperidone-induced retrograde ejaculation. Int Clin Psychopharmacol 2013 May;28(3):156.

(51) Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol 2008 Apr;28(2 Suppl 1):S12-9.

(52) Klinger G, Stahl B, Fusar-Poli P, Merlob P. Antipsychotic drugs and breastfeeding. Pediatr Endocrinol Rev 2013 Mar-Apr;10(3):308-317.

(53) Parikh T, Goyal D, Scarff JR, Lippmann S. Antipsychotic drugs and safety concerns for breast-feeding infants. South Med J 2014 Nov;107(11):686-688.

(54) Stassinos G, Klein-Schwartz W. Asenapine, iloperidone and lurasidone exposures in young children reported to U.S. poison centers. Clin Toxicol (Phila) 2017 Oct 10:1-5.

(55) Muzyk AJ, Cvelich RG, Kincaid BR, Preud'homme XA. Angioedema occurring in patient prescribed iloperidone and haloperidol: a cross-sensitivity reaction to antipsychotics from different chemical classes. J Neuropsychiatry Clin Neurosci 2012 Spring;24(2):E40-1.

(56) Guanci N, Aggarwal R, Schleifer S. Atypical neuroleptic malignant syndrome associated with iloperidone administration. Psychosomatics 2012 Nov-Dec;53(6):603-605.

(57) Naglich AC, Nelson LA, Hornstra R,Jr. Two Cases of Iloperidone-Related Tardive Dyskinesia. J Clin Psychopharmacol 2016 Dec;36(6):742-743.

(58) Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol 2014 May;10(5):721-746.

(59) Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. J Manag Care Pharm 2012 Jun;18(5 Suppl B):S1-20.

(60) Amon J, Stephen E, El-Mallakh RS. A case of iloperidone overdose in a 27-year-old man with cocaine abuse. SAGE Open Med Case Rep 2016 Aug 8;4:2050313X16660485.

(61) Lavedan C, Licamele L, Volpi S, Hamilton J, Heaton C, Mack K, et al. Association of the NPAS3 gene and five other loci with response to the antipsychotic iloperidone identified in a whole genome association study. Mol Psychiatry 2009 Aug;14(8):804-819.

(62) Volpi S, Potkin SG, Malhotra AK, Licamele L, Lavedan C. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. J Clin Psychiatry 2009 Jun;70(6):801-809.

(63) Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag 2017 Jun 29;13:757-777.

(64) Ponizovsky AM, Marom E, Ben-Laish M, Barash I, Weizman A, Schwartzberg E. Trends in the use of antipsychotics in the Israeli inpatient population, 2004-2013. Isr J Health Policy Res 2016 Jun 15;5:16-016-0074-7. eCollection 2016.

(65) Citrome L. A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: an evidence-based medicine approach. CNS Drugs 2013 Nov;27(11):879-911.

(66) Bishop JR, Bishop DL. Iloperidone for the treatment of schizophrenia. Drugs Today (Barc) 2010 Aug;46(8):567-579.

(67) Hasnain M, Vieweg WV, Hollett B. Weight gain and glucose dysregulation with second-generation antipsychotics and antidepressants: a review for primary care physicians. Postgrad Med 2012 Jul;124(4):154-167.

(68) Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol 2008 Apr;28(2 Suppl 1):S4-11.

(69) Stahl SM. Role of alpha1 adrenergic antagonism in the mechanism of action of iloperidone: reducing extrapyramidal symptoms. CNS Spectr 2013 Dec;18(6):285-288.

(70) Dargani NV, Malhotra AK. Safety profile of iloperidone in the treatment of schizophrenia. Expert Opin Drug Saf 2014 Feb;13(2):241-246.

(71) Bobo WV. Asenapine, iloperidone and lurasidone: critical appraisal of the most recently approved pharmacotherapies for schizophrenia in adults. Expert Rev Clin Pharmacol 2013 Jan;6(1):61-91.

(72) Rado J, Janicak PG. Pharmacological and clinical profile of recently approved second-generation antipsychotics: implications for treatment of schizophrenia in older patients. Drugs Aging 2012 Oct;29(10):783-791.