CNS Spectrums (2020), **25**, 128–135.
doi:10.1017/S1092852919000841

REVIEW ARTICLE

Dopamine antagonist antipsychotics in diverted forensic populations

Michael A. Cummings,[1,2]* *George J. Proctor,*[3] *and Ai-Li W. Arias*[2]

[1] Department of Psychiatry, University of California, Riverside, CA, USA
[2] Department of Psychiatry, University of California, Irvine, Patton, CA 92369, USA
[3] Department of Psychiatry, Loma Linda University School of Medicine, Patton, CA 92369, USA

In community settings, negative symptoms and cognitive deficits are the primary barriers to independent living, stable relationships, and employment for individuals suffering from schizophrenia-spectrum disorders. In contrast, however, positive psychotic symptoms (e.g., command hallucinations and persecutory delusions) often drive behavior which serves as the gateway to arrest and criminalization. Historically, the keystone of treatment for positive psychotic symptoms has been antagonism of dopamine D2 receptors in the mesolimbic tract. In this article, we review and explore the principles underlying dopamine antagonism for the treatment of psychosis; optimization of dopamine antagonists in treating positive psychotic symptoms; the advantages of depot dopamine antagonist antipsychotics in forensic settings; the concepts of pharmacokinetic and pharmacodynamic treatment failures; and the role of medication plasma concentrations in optimizing and managing treatment.

Received 16 January 2019; Accepted 23 February 2019; First published online 7 May 2019

Key words: Dopamine antagonists, decriminalization, long-acting antipsychotics, positive symptoms, schizophrenia.

Introduction

In community settings, the principle barriers to independent living, stable relationships, and gainful employment arise from the negative and cognitive symptom domains of schizophrenia-spectrum disorders.[1,2] In contrast, the positive symptoms of psychosis often are the gateway (e.g., via persecutory delusion associated with anger) to arrest and criminalization for the mentally ill.[3,4] Since the clinical discovery of chlorpromazine in 1952, dopamine antagonism in the mesolimbic dopamine circuit has been central to treating the positive symptoms of psychosis.[5,6] The hyperactivity of the mesolimbic circuit and the normalizing effects of the dopamine antagonist antipsychotics are illustrated in Figure 1.

In this review, we seek to understand the roles of dopamine antagonist antipsychotics, including the use of long-acting or depot formulations and plasma concentrations, in controlling the positive symptoms of psychosis, thereby supporting decriminalization of those suffering from psychotic disorders.[7]

Principle Text

The French pharmaceutical firm, Rhône-Poulenc, began exploring polycyclic antihistamine compounds in 1933. This led to the approval and clinical introduction of diphenhydramine in 1946. Promethazine, a phenothiazine derivative, was approved the following year. Although this compound produced sedation, decreased motor activity, and indifference to stimulation in rats, it had much more limited effects in humans.

In 1948, a French surgeon named Pierre Huguenard began using a combination of promethazine and pethidine (a.k.a. meperidine), an opioid, as preoperative medications to calm and sedate patients. Henry Laborit, another French surgeon, subsequently proposed to Rhône-Poulenc that a more effective replacement for promethazine be sought. Consequently in December 1950, the chemist Paul Charpentier produced various compounds related to promethazine, including RP-4560 or chlorpromazine.

Chlorpromazine appeared to be the most promising compound because of its lesser peripheral effects.

*Address correspondence to: Michael A. Cummings, Administrative Annex # 159, Department of State Hospitals – Patton, 3102 East Highland Avenue, Patton, CA 92369, USA (Email: Michael.Cummings@DSH.CA.GOV).

The authors wish to thank Ms. Tina Lache for her assistance in proofing and formatting this article.

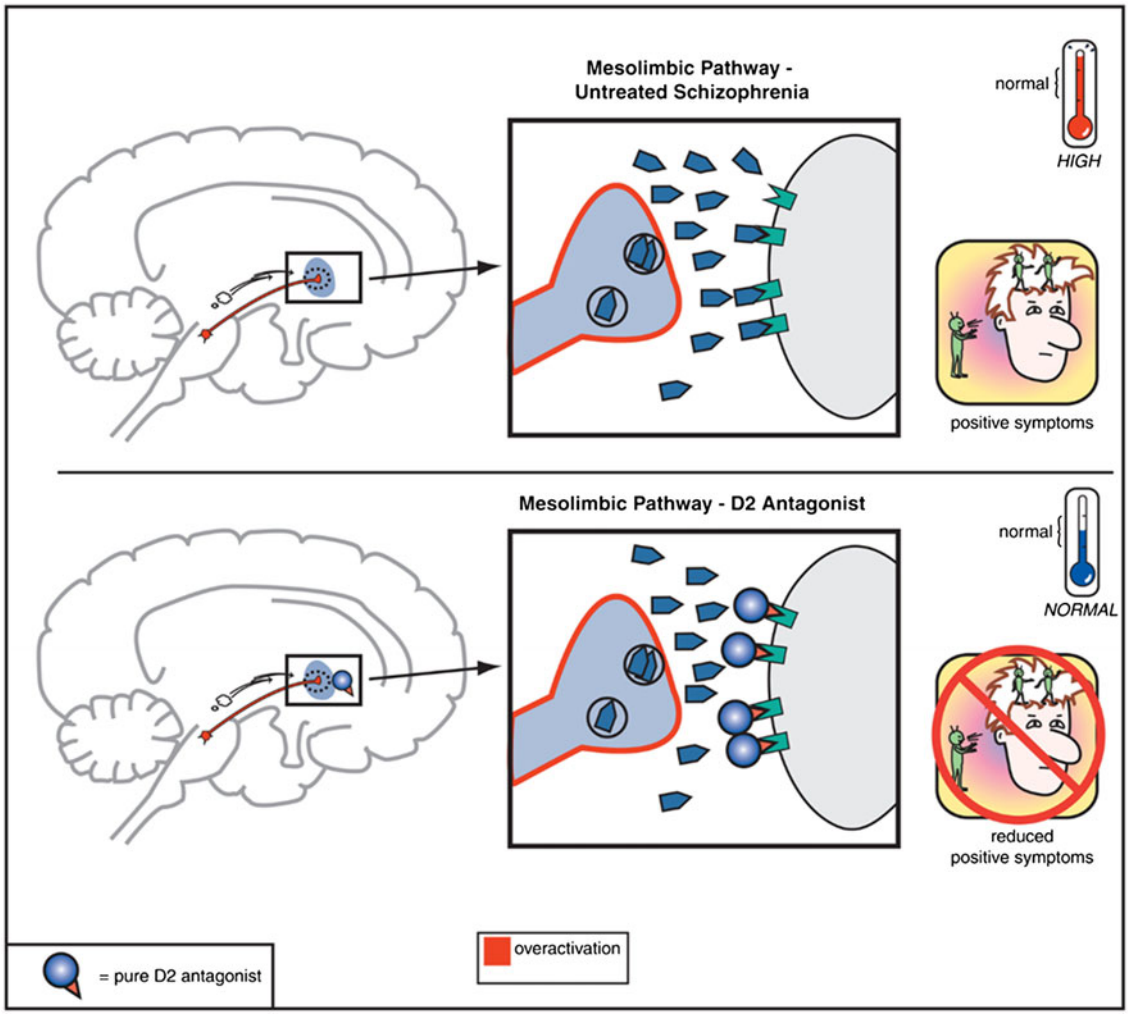

FIGURE 1. Mesolimbic pathway and D2 antagonists.

Chlorpromazine was distributed for testing in humans between April and August 1951. In this context, Henry Laborit tested chlorpromazine at the Val-de-Grâce Military Hospital in Paris. Dr. Laborit found the drug effective, as it produced a state akin to artificial hibernation. In fact, Dr. Laborit became such a proponent of chlorpromazine that it became colloquially known as "Laborit's drug."

Nevertheless, chlorpromazine's use as a preoperative drug was cut short by its propensity to induce orthostatic hypotension and syncope via antagonism at α-adrenergic receptors. Despite this failure, a French psychiatrist named Pierre Deniker had been aware of chlorpromazine and was interested in using it to calm psychotic and manic patients at St. Anne's Hospital in Paris. Dr. Deniker's application of chlorpromazine to psychiatric patients was supported by Professor Jean Delay, who was the superintendent of St. Anne's during that time. Treatment with chlorpromazine proved more successful than Dr. Deniker and Dr. Delay had hoped. It reduced positive psychotic symptoms such as delusional ideation and hallucinations. Additionally, it calmed agitated and regressed behaviors while promoting emotional stability. Consequently, the success of chlorpromazine in psychiatry was likened to the discovery of antibiotics with respect to medical importance. Chlorpromazine's achievement led to the development of first-generation antipsychotics, several of which continue to be used clinically today (see Table 1).[8]

Clozapine, the first second-generation antipsychotic, was synthesized by Schmuts and Eichenberger in 1958. It has since become the gold standard for the management of treatment-resistant schizophrenia and pointed to pathological mechanisms in schizophrenia-spectrum disorders beyond dysregulation of dopamine (i.e., glutamate hypoactivity and, perhaps, muscarinic hypoactivity).[9] The success of clozapine and its difficult adverse effect profile ignited substantial research in pursuit of antipsychotics that would be as effective as clozapine but with an improved safety profile.[10] This plethora of research

https://doi.org/10.1017/S1092852919000841 Published online by Cambridge University Press

TABLE 1. First-generation dopamine antagonists

Medication Generic Name	Chemical Group	Comments
Acepromazine	Phenothiazine	Used primarily in veterinary medicine
Benperidol	Butyrophenone	
Bromperidol	Butyrphenone	
Carpipramine	Tricyclic	
Chlorpromazine	Phenothiazine	First antipsychotic
Chlorprothixene	Thiothixene	
Clocapramine	Tricyclic	
Clopenthixol	Thiothixene	
Clorotepine	Tricyclic	
Clotiapine	Tricyclic	
Compazine	Phenothiazine	Used as antiemetic
Cyamemazine	Phenothiazine	
Dixyrazine	Phenothiazine	
Droperidol	Butyrophenone	Used primarily for anesthesia
Flupenthixol	Thioxanthene	
Fluphenazine	Phenothiazine	Available as long-acting injectable
Fluspirilene	Diphenylbutylpiperidine	
Haloperidol	Butyrophenone	Available as long-acting injectable
Levomepromazine	Phenothiazine	
Loxapine	Tricyclic	Available as nasal spray
Mesoridazine	Phenothiazine	Discontinued
Molindone	Other	Discontinued
Moperone	Butyrphenone	Discontinued
Mosapramine	Tricyclic	
Pearlapine	Tricyclic	
Penfluridol	Diphenylbutylpiperidine	
Perazine	Phenothiazine	
Pericyazine	Phenothiazine	
Perphenazine	Phenothiazine	
Pimozide	Diphenylbutylpiperidine	Prone to QT prolongation
Pipamperone	Butyrphenone	Discontinued
Pipotiazine	Phenothiazine	
Prochlorperazine	Phenothiazine	
Promazine	Phenothiazine	Discontinued
Promethazine	Phenothiazine	Antipsychotic precursor
Prothipendyl	Phenothiazine	
Sulpiride	Benzamide	
Sultopride	Benzamide	
Thioproperazine	Phenothiazine	Available in Canada only among English-speaking countries
Thioridazine	Phenothiazine	Discontinued
Thiothixene	Thioxanthene	
Timiperone	Butyrphenone	
Trifluoperazine	Phenothiazine	
Triflupromazine	Phenothiazine	Discontinued
Veralipride	Benzamide	
Zuclopenthixol	Thioxanthene	

Notes: Derived from the U.S. and E.U. Pharmacopeias (WWW.USP.ORG and WWW.EDQM.EU)
Red indicates those medications in common use in the United States.

resulted in the synthesis and approval of several second-generation dopamine antagonists (see Table 2).[11]

Mechanisms

Despite various chemical subtypes, a wide range of potencies at dopamine D2 receptors and important differences in side-effect profiles based on affinities for and actions at other receptors (i.e., adrenergic, histamine, acetylcholine, serotonin receptors, etc.), all of the dopamine antagonist antipsychotics share a principle mechanism for exerting their antipsychotic effects, namely, induction of depolarization blockade at the dopamine neurons that give rise to the mesolimbic dopamine pathway.[12] For the first-generation antipsychotics, this depolarization blockade accounted for circa 92% to 93% of antipsychotic efficacy

https://doi.org/10.1017/S1092852919000841 Published online by Cambridge University Press

TABLE 2. Second-generation dopamine antagonists

Medication Generic Name	Chemical Group	Comments
Amisulpride	Benzamide	
Asenapine	Tricyclic	Available as orally dissolving tablet only
Blonanserin	Other	
Iloperidone	Benzisoxazole/ Benzisothiazole	
Lurasidone	Benzisoxazole/ Benzisothiazole	Effective for bipolar depression
Melperone	Butyrphenone	
Nemonapride	Benzamide	
Olanzapine	Tricyclic	Modest glutamate modulation at high plasma concentrations (>120 ng/ml)
Paliperidone	Benzisoxazole/ Benzisothiazole	Available in controlled release and long-acting injectable formulations
Perospirone	Benzisoxazole/ Benzisothiazole	
Quetiapine	Tricyclic	Metabolite effective for bipolar depression
Remoxipride	Benzamide	
Risperidone	Benzisoxazole/ Benzisothiazole	Available in long-acting injectable formulation
Sertindole	Other	
Ziprasidone	Benzisoxazole/ Benzisothiazole	
Zotepine	Tricyclic	

Notes: Derived from the U.S. and E.U. Pharmacopeias (WWW.USP.ORG and WWW.EDQM.EU)
Red indicates commonly in use in the U.S.

TABLE 3. Optimal plasma concentration ranges for selected dopamine antagonist antipsychotics

Antipsychotic	Optimal Trough Plasma Concentration Range
Fluphenazine	0.8–2.0 ng/ml in most patients 2.0–4.0 ng/ml in more ill patients
Haloperidol	5.0–20.0 ng/ml in most patients 20.0–30.0 ng/ml in more ill patients
Olanzapine	40–120 ng/ml in most patients 120–200 ng/ml in more ill patients
Paliperidone	28–112 ng/ml
Perphenazine	0.8–4.0 ng/ml

Note: Derived from the California Department of State Hospitals Psychotropic Medication Policy, Chapter 41, Appendix – Therapeutic Plasma Concentrations for Antipsychotics and Mood Stabilizers (2019).

for these drugs.[13] Among the second-generation antipsychotics, dopamine antagonism and depolarization blockade remains the likely principle mechanism of action, although some (e.g., olanzapine) may exert modest antipsychotic effects via the modulation of glutamate signal transduction.[14] In this context, clozapine is unique in that it likely provides little, if any, of its antipsychotic efficacy via direct effects on dopamine signaling, instead more likely acting via robust modulation of glutamate.[15] Thus, the first step in treating positive psychotic symptoms is to provide the patient with an adequate exposure to the initial chosen dopamine antagonist antipsychotic for an adequate amount of time.

Antipsychotic Trials

A recent consensus paper identified the parameters of an adequate antipsychotic trial as a trial of at least 6 weeks duration and a dose of at least 600 mg chlorpromazine equivalents. A duration of 4 months was given for long-acting injectable antipsychotics. Because medication adherence is often poor, this paper held a single antipsychotic plasma concentration measurement to be a minimal standard, while a more optimal standard was held to be two plasma concentration measurements separated by at least 2 weeks without prior notification of the patient. A further important principle of adequate antipsychotic trials is pursuit of the trial until one of three endpoints is achieved: improvement of psychotic signs and symptoms; emergence of intolerable adverse effects that cannot be managed via reasonable interventions; or, a point of futility is reached, for example, saturation of D2 dopamine receptors or flattening of the drug's receptor occupancy curve.[16]

Importantly, failure to achieve a 20% to 30% reduction in psychotic symptoms in response to two or more adequate dopamine antagonist trials indicates that the patient is treatment-resistant; that is, the patient exhibits a pharmacodynamic failure in response to adequate dopamine antagonism. Additionally, such treatment resistance portends a poor probability of response to most antipsychotic agents. Most first- and second-generation antipsychotic medications show a response rate of 0% to 5% among such patients, while high plasma concentration olanzapine (120–200 ng/ml) produces a response rate of about 7%.[17] Moreover, data suggest for treatment-resistant schizophrenic patients that responsiveness to even clozapine begins to decline at about 2.8 years of treatment-resistant status.[18] The low probability of response to antipsychotics other than clozapine combined with data indicating a response-decay curve to even clozapine after 2.8 years among treatment-resistant schizophrenia-spectrum disordered patients argues strongly in favor of clozapine treatment as soon as strictly defined treatment resistance is identified. That is, further time should not be wasted in pursuing treatments with a low probability of success, thereby

https://doi.org/10.1017/S1092852919000841 Published online by Cambridge University Press

TABLE 4. LAI dopamine antagonist antipsychotic initiation

LAI Antipsychotic	Comments on Initiation
Fluphenazine	For each 10 mg of oral fluphenazine per day, prescribe 25 mg of fluphenazine decanoate I.M. q week times three and then continue for every 2 weeks at 12.5 mg to a maximum of 100 mg as guided by plasma concentration measurements. Optimal for most patients is 0.8–2.0 ng/ml. Some more treatment-resistant patients may require plasma concentrations of 2.0–4.0 ng/ml. Note that fluphenazine decanoate exhibits both an immediate and delayed release from its vehicle, requiring initial reduction or discontinuation of oral dosing in some individuals to avoid post-injection emergence of neurologic adverse effects.
Haloperidol	Because haloperidol decanoate has little immediate release phase, a loading dose strategy is required to avoid a need for prolonged co-administration of an oral antipsychotic. That is, administration at a fixed dose would require 3–5 months to reach steady-state. Give 100–300 mg I.M. q 1-week times two to three doses. For each 100 mg used in loading, the average steady-state plasma concentration is 7.75 ng/ml. Measurement of a plasma concentration before the third loading dose will assist in determining whether the third loading dose is needed. Measurement of a plasma concentration shortly before the first maintenance dose will be helpful in fine tuning ongoing dosing. Optimal for most patients is 5–20 ng/ml. A few more treatment-resistant patients may require plasma concentrations of 20–30 ng/ml. Adverse neurological effects become more frequent at plasma concentrations >20 ng/ml. Maintenance dosing should begin 14 days after the last loading injection. For maintenance, give on average 100 mg q 4 weeks per 20 mg of the prior oral haloperidol daily dose. If the maintenance dose exceeds 300 mg, then divide the dose and administer every 14 days, as the maximum injectable volume is 3 ml.
Olanzapine	LAI olanzapine is available in 150, 210, 300, and 405 mg doses. Oral equivalents have not been established. There is no need for oral cross-over or loading. Note, however, that a circa 0.1% risk of delirium, obtundation, and coma follows each dose. Direct nursing observation is required for a minimum of 3 h following each injection.
Paliperidone	Give an initial dose of 234 mg followed by a second initiation dose of 156 mg after 1 week. Initial doses should be deltoid. Maintenance doses may be deltoid or gluteal. The modal maintenance dose is 117 mg q 4 weeks, with a dose range of 39–234 mg. A dose of 234 mg per month produces 9-hydroxy-risperidone plasma concentrations comparable to 4–5 mg of oral risperidone per day (risperidone + 9-hydroxy-risperidone). Oral risperidone or paliperidone is not required after the initiation phase. Paliperidone palmitate extended-release (Invega Trinza®) is restricted to patients who have received effective and stable treatment with paliperidone palmitate (Invega Sustenna®) for a minimum of four (4) months. At the time, the next dose of paliperidone palmitate would be due, give the equivalent dose of paliperidone palmitate extended-release (Invega Trinza®)
Risperidone	Initiate depot risperidone (Consta®) at 25–50 mg. q 2 weeks, while continuing oral risperidone treatment. After 3 weeks have passed since the initial injection, taper and discontinue oral risperidone treatment. Each 25 mg of LAI risperidone produces plasma concentrations of risperidone + 9-hydroxy-risperidone comparable to 2 to 3 mg of oral risperidone. Risperidone also is available in a subcutaneous formulation (Perseris®) can be given in abdominal subcutaneous injections of 90 mg (0.6 ml) or 120 mg (0.8 ml), achieving plasma concentrations comparable to 3 or 4 mg of oral risperidone, respectively, at about 1 week, obviating the need for oral cross-over. Injections of this formulation are monthly.

Notes: Derived from the California Department of State Hospitals Psychotropic Medication Policy, Chapter 09, Depot Antipsychotics (2019). Also derived from package inserts for olanzapine (Zyprexa Relprevv®), paliperidone (Invega Sustenna® and Invega Trinza®), and risperidone (Risperdal Consta®), as well as references 40, 41, 42, and 43. Web sites: WWW.DrugInserts.COM/lib/rx/meds/Zyprexa-Relprevv-1; WWW.InvegaSustenna.COM; WWW.InvegaTrinza.COM; and, WWW.DrugInserts.COM/lib/rx/meds/Risperdal-Consta-1.

diminishing even the superior efficacy of clozapine in patients who are pharmacodynamic failures with respect to dopamine antagonism.[19,20]

In the context of treatment-resistant schizophrenia, it is also worth noting that although there are a number of augmentation strategies ranging from antipsychotic polypharmacy to addition of medications from additional classes, the effect sizes of these strategies have been described as small or modest.[21] Exceptions to this analysis include augmentation with mood stabilizers in schizophrenic patients exhibiting early acute psychomotor agitation or in patients exhibiting a mood component or bipolar diathesis.[22-24] It is also worth noting that dopamine partial agonist antipsychotics may be more effective for the negative and cognitive symptom domains of schizophrenia-spectrum disorders than the positive symptom domain.[25-27]

The second route to treatment failure for the dopamine antagonists is pharmacokinetic. In general, data have suggested that for the dopamine antagonists, optimal antipsychotic response occurs when dopamine D2 and D3 receptor occupancies are roughly in the 60% to 80% range.[28] This is why assuring adequate receptor occupancy for an adequate period of time is critical to providing an adequate dopamine antagonist trial.[14] In this context, it is worth noting that plasma concentrations of the antipsychotics correlate much more tightly with relevant receptor occupancies than the prescribed dose.[29] Numerous factors can affect the relationship between dose and plasma concentration, including adherence, absorption, distribution, catabolism, and elimination.[30] Hence, measuring antipsychotic plasma concentrations provides a much more precise and accurate means to assuring adequate receptor occupancy. (Please see the companion article in this issue entitled, "Monitoring and Improving Antipsychotic Adherence in Outpatient Forensic Diversion Programs," by Meyer, J.M.)

https://doi.org/10.1017/S1092852919000841 Published online by Cambridge University Press

Optimal plasma concentration ranges for selected dopamine antagonist antipsychotics are shown in Table 3.[31,22]

Measuring plasma antipsychotic concentrations can be useful in various clinical circumstances ranging from benchmarking an optimal clinical response to assessing poor or extensive metabolism or investigating the clinical decompensation of a previously stable patient.[32]

While patient factors such as drug absorption, distribution, catabolism, and elimination play important roles in determining antipsychotic efficacy, they often pale in importance when compared with medication adherence.[33] This is especially true in forensic settings, where medication diversion often becomes an added challenge.[34] The use of long-acting injectable (LAI) antipsychotics provides the most reliable means to address issues of non-adherence or diversion.[35] Because decriminalizing a portion of the arrested mentally ill population would involve release to community settings, assurance of continued treatment becomes a critical requirement for the success of any such program.[36] Additionally, it is worth noting that LAI antipsychotics have been associated with decreased rates of violence and criminality when compared with their oral counterparts.[37] In fact, the benefits of LAI antipsychotics are such that they produce an approximately 30% reduction in mortality risk when compared with the same antipsychotics prescribed in oral formulations in schizophrenia-spectrum disordered patients.[38]

Unfortunately, LAI antipsychotics are infrequently used and thus are less familiar.[39] In particular, clinicians may be unfamiliar with strategies for initiating LAI antipsychotic treatment or transitioning from oral to depot formulations of dopamine antagonist antipsychotics.[40–43] Initiation/transition strategies are summarized in Table 4.

Conclusions

While negative and cognitive psychotic symptoms are major barriers to successful social functioning and employment in the community at large, it is more often positive psychotic symptoms that result in behaviors that lead to arrest and criminalization. Dopamine antagonist antipsychotics provide the cornerstone of treatment for positive psychotic symptoms and may provide an effective means to divert the mentally ill from the path of criminalization and incarceration. Critical to their success, however, are antipsychotic trials of therapeutic dose/plasma concentration for an adequate period of time. Moreover, such medication trials should be pursued to one of three endpoints: (1) successful improvement of psychotic signs and symptoms; (2) emergence of intolerable adverse effects that do not respond to reasonable interventions; or (3) arrival at a point of futility (e.g., saturation of D2 dopamine receptors or flattening of the medication's receptor occupancy curve).

In those patients who have pharmacodynamic failures of two adequate trials of first- or second-generation dopamine antagonist antipsychotics, a trial of clozapine should be pursued vigorously. This is true because other antipsychotics, with or without augmentation, are unlikely to produce an adequate response in patients with strictly defined treatment-resistant schizophrenia. Moreover, some data indicate that even clozapine's efficacy in this context begins to fade after treatment resistance has been present for 2.8 years. Thus, our treatment-resistant schizophrenia patients would be better served if we clinicians do not waste time pursuing multiple antipsychotic trials or seemingly endless augmentation trials which are not likely to be successful.

With respect to pharmacokinetic failures, it should be emphasized that plasma concentrations are a much better means to assess antipsychotic trial adequacy than medication dose. In this context, it must be acknowledged that the failure of medication adherence is a major cause of pharmacokinetic failure. In short, if the medication does not make it into the patient, then there is no hope for an adequate antipsychotic response. Moreover, the issue of adherence is especially important to decriminalization of the mentally ill, as such individuals would return to the community as an inherent goal of decriminalization. To date, the only formulations of the antipsychotics that we clinicians can be certain are reliably making it into the patient on an ongoing basis are the long-acting injectable antipsychotics. In fact, data indicate that these formulations produce superior antipsychotic responses and even reduce mortality when compared with their oral counterparts. They are nevertheless underutilized, often being thought of as medications "of last resort". Instead, the available data support that the long-acting injectable antipsychotics should be one of our most frequently used tools, especially in forensic populations.

Disclosure

Dr. Cummings, Dr. Proctor, and Dr. Arias declare that they have nothing to disclose.

REFERENCES:

1. Grove TB, Tso IF, Chun J, *et al.* Negative affect predicts social functioning across schizophrenia and bipolar disorder: findings from an integrated data analysis. *Psychiatry Res*. 2016; **243**: 198–206. doi: 10.1016/j.psychres.2016.06.031
2. Kaneko K. Negative symptoms and cognitive impairments in schizophrenia: two key symptoms negatively influencing social functioning. *Yonago Acta Medica*. 2018; **61**(2): 91–102.
3. Ullrich S, Keers R, Coid JW. Delusions, anger, and serious violence: new findings from the MacArthur violence risk assessment study. *Schizophr Bull*. 2014; **40**(5): 1174–1181. doi: 10.1093/schbul/sbt126

https://doi.org/10.1017/S1092852919000841 Published online by Cambridge University Press

4. Fazel S, Zetterqvist J, Larsson H, Langstrom N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet (London, England)* 2014; **384**(9949): 1206–1214. doi: 10.1016/s0140-6736(14)60379-2
5. Urs NM, Peterson SM, Caron MG. New concepts in Dopamine D2 receptor biased signaling and implications for Schizophrenia therapy. *Biol Psychiatry*. 2017; **81**(1): 78–85. doi: 10.1016/j.biopsych.2016.10.011
6. Howes OD, McCutcheon R, Owen MJ, Murray RM. The role of genes, stress, and dopamine in the development of Schizophrenia. *Biol Psychiatry*. 2017; **81**(1): 9–20. doi: 10.1016/j.biopsych.2016.07.014
7. Rotter M, Carr WA. Targeting criminal recidivism in mentally ill offenders: structured clinical approaches. *Community Ment Health J*. 2011; **47**(6): 723–726. doi: 10.1007/s10597-011-9391-z
8. Lopez-Munoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of chlorpromazine. *Ann Clin Psychiatry*. 2005; **17**(3): 113–135.
9. Melkersson K, Lewitt M, Hall K. Higher serum concentrations of tyrosine and glutamate in schizophrenia patients treated with clozapine, compared to in those treated with conventional antipsychotics. *Neuro Endocrinology Letters*. 2015; **36**(5): 465–480.
10. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. *History of Psychiatry*. 2007; **18**(1): 39–60. doi: 10.1177/0957154x07070335
11. Shen WW. A history of antipsychotic drug development. *Compr Psychiatry*. 1999; **40**(6): 407–414.
12. Grace AA. The depolarization block hypothesis of neuroleptic action: implications for the etiology and treatment of schizophrenia. *J Neural Transm Suppl*. 1992; **36**: 91–131.
13. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry*. 2005; **10**(1): 79–104. doi: 10.1038/sj.mp.4001556
14. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol (Oxf)*. 2015; **29**(2): 97–115. doi: 10.1177/0269881114563634
15. Veerman SR, Schulte PF, de Haan L. The glutamate hypothesis: a pathogenic pathway from which pharmacological interventions have emerged. *Pharmacopsychiatry* 2014; **47**(4–5): 121–130. doi: 10.1055/s-0034-1383657
16. Howes OD, McCutcheon R, Agid O, *et al.* Treatment-resistant Schizophrenia: treatment response and resistance in Psychosis (TRRIP) Working Group Consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017; **174**(3): 216–229. doi: 10.1176/appi.ajp.2016.16050503
17. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. *Am J Psychiatry*. 2016; **173**(2): 166–173. doi: 10.1176/appi.ajp.2015.15030332
18. Yoshimura B, Yada Y, So R, Takaki M, Yamada N. The critical treatment window of clozapine in treatment-resistant schizophrenia: secondary analysis of an observational study. *Psychiatry Res*. 2017; **250**: 65–70. doi: 10.1016/j.psychres.2017.01.064
19. Kerwin R. When should clozapine be initiated in schizophrenia?: some arguments for and against earlier use of clozapine. *CNS Drugs*. 2007; **21**(4): 267–278. doi: 10.2165/00023210-200721040-00002
20. Doyle R, Behan C, O'Keeffe D, *et al.* Clozapine use in a cohort of first-episode psychosis. *J Clin Psychopharmacol*. 2017; **37**(5): 512–517. doi: 10.1097/jcp.0000000000000734
21. Galling B, Roldan A, Hagi K, *et al.* Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*. 2017; **16**(1): 77–89. doi: 10.1002/wps.20387
22. Stahl SM, Morrissette DA, Cummings M, *et al.* California state hospital violence assessment and treatment (Cal-VAT) guideline. *CNS Spectrums*. 2014; **19**(5): 449–465.
23. Fond G, Boyer L, Favez M, *et al.* Medication and aggressiveness in real-world schizophrenia. Results from the FACE-SZ dataset. *Psychopharmacology* 2016; **233**(4): 571–578. doi: 10.1007/s00213-015-4167-8
24. Garriga M, Pacchiarotti I, Kasper S, *et al.* Assessment and management of agitation in psychiatry: expert consensus. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*. 2016; **17**(2): 86–128. doi: 10.3109/15622975.2015.1132007
25. Mossaheb N, Kaufmann RM. Role of aripiprazole in treatment-resistant schizophrenia. *Neuropsychiatric Disease and Treatment*. 2012; **8**: 235–244. doi: 10.2147/ndt.S13830
26. Veerman SRT, Schulte PFJ, de Haan L. Treatment for negative symptoms in schizophrenia: a comprehensive review. *Drugs*. 2017; **77**(13): 1423–1459. doi: 10.1007/s40265-017-0789-y
27. Stahl SM. Drugs for psychosis and mood: unique actions at D3, D2, and D1 dopamine receptor subtypes. *CNS Spectrums*. 2017; **22**(5): 375–384. doi: 10.1017/s1092852917000608
28. Wulff S, Pinborg LH, Svarer C, *et al.* Striatal D(2/3) binding potential values in drug-naive first-episode schizophrenia patients correlate with treatment outcome. *Schizophr Bull*. 2015; **41**(5): 1143–1152. doi: 10.1093/schbul/sbu220
29. Urban AE, Cubala WJ. Therapeutic drug monitoring of atypical antipsychotics. *Psychiatr Pol*. 2017; **51**(6): 1059–1077. doi: 10.12740/pp/65307
30. Fan J, de Lannoy IA. Pharmacokinetics. *Biochem Pharmacol*. 2014; **87**(1): 93–120. doi: 10.1016/j.bcp.2013.09.007
31. Meyer JM, Cummings MA, Proctor G, Stahl SM. Psychopharmacology of persistent violence and aggression. *Psychiatr Clin North Am*. 2016; **39**(4): 541–556. doi: 10.1016/j.psc.2016.07.012
32. Dahl SG. Plasma level monitoring of antipsychotic drugs. Clinical utility. *Clin Pharmacokinet*. 1986; **11**(1): 36–61. doi: 10.2165/00003088-198611010-00003
33. Tharani AJ, Farooq S, Saleem F, Naveed A. Compliance to antipsychotic medication: a challenge for client, family and health care providers. *JPMA J Pak Med Assoc*. 2013; **63**(4): 516–518.
34. Pilkinton PD, Pilkinton JC. Prescribing in prison: minimizing psychotropic drug diversion in correctional practice. *Journal of Correctional Health Care: The Official Journal of the National Commission on Correctional Health Care* 2014; **20**(2): 95–104. doi: 10.1177/1078345813518629
35. Marcus SC, Zummo J, Pettit AR, Stoddard J, Doshi JA. Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge. *Journal of Managed Care and Specialty Pharmacy*. 2015; **21**(9): 754–768. doi: 10.18553/jmcp.2015.21.9.754
36. McGuire AB, Bond GR. Critical elements of the crisis intervention team model of jail diversion: an expert survey. *Behav Sci Law*. 2011; **29**(1): 81–94. doi: 10.1002/bsl.941
37. Mohr P, Knytl P, Vorackova V, Bravermanova A, Melicher T. Long-acting injectable antipsychotics for prevention and management of violent behaviour in psychotic patients. *Int J Clin Pract* 2017; **71**(9): e12997. doi: 10.1111/ijcp.12997
38. Taipale H, Mittendorfer-Rutz E, Alexanderson K, *et al.* Antipsychotics and mortality in a nationwide cohort of 29, 823 patients with schizophrenia. *Schizophr Res*. 2017; **197**: 274–280. doi: 10.1016/j.schres.2017.12.010
39. Iyer S, Banks N, Roy MA, *et al.* A qualitative study of experiences with and perceptions regarding long-acting injectable antipsychotics: part II-physician perspectives. *Can J Psychiatry* 2013; **58**(5 Suppl 1): 23s–29s.

40. Siragusa S, Saadabadi A. Fluphenazine. *StatPearls*. Treasure Island (FL): StatPearls Publishing LLC.; 2018.
41. Quraishi S, David A. Depot haloperidol decanoate for schizophrenia. *The Cochrane Database of Systematic Reviews*. **2000**(2): Cd001361. doi: 10.1002/14651858.
42. Park EJ, Amatya S, Kim MS, *et al.* Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia. *Archives of Pharmacal Research*. 2013; **36**(6): 651–659. doi: 10.1007/s12272-013-0105-7
43. Citrome L. Sustained-release Risperidone via subcutaneous injection: a systematic review of RBP-7000 (PERSERIS()) for the treatment of Schizophrenia. *Clinical Schizophrenia Related Psychoses*. **12**(3): 130–141. doi: 10.3371/csrp.Ci.101118