PATIENT FILE

1

Psychotic aggression: the magic combo

The Psychopharmacological Dilemma: Finding biological treatment modalities for reducing psychotic aggression

Jongseung Baek and Seth Judd



Pretest self-assessment question

Which of the following classes of medication should not be considered for long-term adjunct therapy for treatment-resistant schizophrenia (TRS)?

A. Benzodiazepines
B. Mood stabilizers
C. Anticonvulsants
D. Electroconvulsive therapy (ECT)
E. Antidepressants



Patient evaluation on intake

- A male in his late 40s with a long history of schizophrenia, alcohol use disorder (AUD), benzodiazepine use disorder, and cannabis use disorder was transferred to a forensic state hospital for management of psychotic and aggressive behaviors toward himself and others
- The patient showed multiple violent behaviors at the time of hospital admission:
  - He attempted to kick the leg of a staff member who was taking his vitals
  - After sleeping, he went to the restroom and attempted to push his peer
  - He tried to chase after another staff member but was verbally redirected
  - Lastly, he volitionally jumped off his bed backward. He hit the back of his head on the door, sustaining a 3 cm laceration. He reported he was "okay" but refused to talk further
- He declined to answer questions.
- Mental status examination (MSE):
  - General: in hospital attire, fairly kempt
  - Motor: neutral
  - Speech: occasional selective mutism
  - Mood/Affect: "Okay" / neutral and blunted
  - Thought process: linear
  - Thought content: He has urges to assault others in response to auditory hallucination. He denies suicidal and homicidal thoughts

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Insight: limited as noted by his request for addictive substances
- Cognition: below-average intelligence with poor judgment

- It was decided to continue the current regimen of clozapine 300 mg every evening and haloperidol decanoate 250 mg IM every 2 weeks and provide as-needed medications (PRNs) appropriately and judiciously (to avoid drug-seeking behavior)



Psychiatric history

- The patient was diagnosed and treated for schizophrenia in his late teens
  - His primary psychiatric symptoms include auditory hallucinations that command him to harm himself and others
  - His symptoms began a few months after his sibling's suicide
  - He has been on various psychotropic treatment regimens
- He was placed on a state conservatorship shortly after his initial hospitalization
- He has been hospitalized in different levels of mental health facilities
- He previously asked for PRN medicines when he was not outwardly agitated
  - He reported that he wants PRN medicines for the "high"
  - He also reports enjoying being in restraints because it makes him feel "high"
- He previously received ECT but with minimal improvement
- He reported worsening of psychotic symptoms during times of heightened stress



Social and personal history

- He was born in an intact family
- He has three siblings – of whom two are alive
- His mother is deceased and his father is still alive
- He graduated from high school and had sparse employments due to his mental illness
- He has no known history of trauma or abuse
- He has been homeless in between psychiatric placements
- He has a history of multiple substance abuse including benzodiazepines, alcohol, and cannabis
- He has extensive nonviolent and violent criminal history



Medical history

- He had a seizure while taking clozapine 600 mg/day without divalproex
- He developed hypothyroidism and renal insufficiency from lithium toxicity

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Other medical conditions include right retinal detachment, bilateral glaucoma, hypertension, hyperlipidemia, iron deficiency anemia, and stress urinary incontinence



Family history

- He has no family history of mental illnesses



Medication history

- The patient has been on numerous psychotropic medications, including antipsychotics, mood stabilizers, benzodiazepines, and antidepressants
- The following medication amount is the maximum dose per day, unless otherwise stated:
  - Antipsychotics: aripiprazole 15 mg, clozapine 600 mg, fluphenazine 45 mg, haloperidol 350 mg every 2 weeks, olanzapine 50 mg, quetiapine 1200 mg, risperidone 10 mg, ziprasidone 200 mg
  - Antidepressants: bupropion 400 mg, citalopram 40 mg, escitalopram 20 mg, fluoxetine 80 mg, mirtazapine 15 mg, sertraline 100 mg
  - Anticonvulsant/mood stabilizer divalproex 1500 mg, lamotrigine 250 mg, lithium 1200 mg, and valproic acid 1250 mg
- Patient was also prescribed propranolol (60 mg) for akathisia, clonazepam (4 mg) and lorazepam (2 mg) for impulse control
- Adverse reactions: divalproex – pancreatitis; lithium – renal insufficiency



Current medications

- Clozapine 300 mg once every night
- Haloperidol decanoate 250 mg intramuscular (IM) twice monthly
- Hydroxyzine 50 mg three times a day
- Haloperidol 5 mg every 2 hours as needed, but no more than 3 doses per 24 hours
- Levothryroxine 100 ug every day
- Tamsulosin 0.8 mg every night
- Ferrous sulfate 325 mg once every noon
- Metformin once every day
- Multivitamin w/folic acid once every morning
- Lactulose 20 mg every 4 hours as needed for constipation
- Polyethylene glycol 3350 pack once every night

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE



Psychotherapy history

- Due to the presence of ongoing psychotic symptoms and aggressive behaviors, he has been unable to participate in meaningful therapy beyond learning stress management skills (listening to music, taking hot shower, playing the guitar, sitting in his rocking chair, utilizing weighted blanket and essential oils – lavender). He briefly attended sensory modulation therapy



Mechanism of action moment

- Clozapine: atypical antipsychotic
- Target receptors/effect
  - D4 antagonism: high clozapine affinity; however, effect is unknown
  - D_2 antagonist: reduce positive symptoms of psychosis and stabilize affective symptoms
  - $5\text{-}HT_{2A}$ antagonist: enhance dopamine release thus reducing motor side effects and possibly improving cognitive and affective symptoms
  - For some patients, $5\text{-}HT_{2C}$ and $5\text{-}HT_{1A}$ receptor interaction may contribute to efficacy for cognitive and affective symptoms



Attending physician's mental notes

- This patient has tried a variety of antipsychotics with suboptimal results
- His prior history shows frequent decompensation with increased violent tendencies and actions
- There are multiple factors that may be associated with patient's violent behavior
  - Patient reports command auditory hallucinations, which suggests that he was in the state of psychosis when he was acting violently
  - Recent study has shown that patients who experience command auditory hallucinations (CAH) to harm others were twice as likely to be violent as those without CAH
  - This aspect could be controlled by appropriate pharmacotherapy
  - Clozapine and olanzapine are effective in treating aggression stemming from schizophrenia
  - Patient reported urge to inflict self-injury and violence toward others
  - Urge entails impulsivity in the context of strong emotion
  - Impulsivity has been shown to be contributing factor to increased violent behavior
  - This aspect could be addressed through further destressing techniques
- Benzodiazepine PRN for aggression should be avoided, if possible, to prevent reinforcement of drug-seeking behavior

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE



Further investigation

- Is there anything else you would like to know about this patient? What additional information is needed to change or adjust the treatment plan?
  - Clozapine level should be monitored to determine whether it is in therapeutic range. Initially, the patient's clozapine level was 865 mcg/L
  - Dosage was increased to 400 mg to reach maximum therapeutic level of 1000 mcg/L per hospital guidelines
  - For patients on the schizophrenia spectrum and who have failed multiple trials of antipsychotic medications, including clozapine, ECT should be considered. Medical records indicate that he has a history of ECT treatments, but these were discontinued due to lack of response



Case outcome (3 months): use of outcome measures

- The patient continues to exhibit violent behaviors. During the first 2 months, he engaged in over 30 aggressive behaviors per month
- He reports that he is "suffering" from hearing the voices, which he characterizes as "strong" and difficult to resist
- His psychiatric medications were adjusted (clozapine 400 mg every night and haloperidol decanoate 200 mg IM every 2 weeks)
- He is adherent to antipsychotic medications based on plasma level
  - Last clozapine level was 1000 mcg/L which is at the maximum therapeutic level per hospital policy
- The Mini-Mental State Examination was administered and he obtained 21/30 which is suggestive of mild cognitive impairment. However …
  - His impaired vision partially explains the lower score – he had difficulty completing the part of the examination that requires visual acuity
  - He was also drowsy during the session as he had just received a PRN medication



Attending physician's mental notes: first interim progress report

- The patient is taking the highest dose of clozapine, confirmed by plasma level, with modest benefit
- Following adjunct therapy must be considered
  - Previous research has shown small benefit when clozapine is augmented with secondary antipsychotics; however, recent meta-analysis showed no benefit with risperidone (most-used augmentation)

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Although previous meta-analysis research has shown small benefit when clozapine is augmented with a mood stabilizer such as lamotrigine, the difference was no longer statistically significant after removing an outlier
- Out of the available antidepressants, only citalopram has been shown to have improvement in a small study
- ECT adjunct has efficacy rates ranging from 40% to 70% in TRS
- Repetitive transcranial magnetic stimulation (rTMS) has shown evidence of treating auditory hallucination and potential negative symptoms; however, it is not yet FDA approved for treating schizophrenia
- Lastly, deep brain stimulation (DBS) is supported by case studies

- Records indicate the patient had trials of adjunct secondary antipsychotics, mood stabilizers, antidepressants, and ECT without much improvement



Further investigation

- Which adjunct therapy should be considered? What additional information do you need to choose adjunct therapy?
  - Although previous ECT trials showed subpar responses, they were performed under suboptimal clozapine treatment. With optimal clozapine therapy, ECT treatments could improve his psychotic symptoms
  - Other "failed" adjunct therapy could be reconsidered if the concurrent clozapine level was not at the maximum therapeutic level



Case outcome: interim follow-up progress report 6 months

- Patient began receiving three ECT treatments per week
  - ECT team was unable to elicit a seizure until energy level increased to 100%. Changes in the general anesthetic were also made to lower seizure threshold in order to produce a seizure. Methohexital dose was reduced, and ketamine was added, but patient did not tolerate the ketamine well. Anesthesiologist then switched from methohexital to etomidate, a pro-seizure anesthetic. IV caffeine was also added and titrated up to 540 mg
- Patient has been responding positively with ECT treatment, showing a decrease in aggressive behaviors from over 30 incidents over 90 days pre-ECT, to fewer than 5 aggressions per month for the past 3 months
- He reports that he is "doing better" and denies auditory hallucination and thoughts of harming self and others
- His main complaint is his worsening vision from retinal detachment

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Given his improvement, ECT frequency was reduced. However, shortly afterward the frequency of the patient's psychotic behaviors increased. The patient then went back to receiving ECT three times a week
- During recent ECT treatments, ECT nurses and anesthesiologist noted that it was becoming increasingly difficult to obtain intravenous (IV) access
  - Larger-gauge needles on more peripheral veins were used but patient reports pain when receiving caffeine IV
- Clozapine level was rechecked. At 400 mg, the level was 1480 mcg. Patient did not show any signs of clozapine toxicity, such as seizures, arrhythmia, cardiotoxicity, or neutropenia. Dose was reduced to 350 mg and follow-up level was in therapeutic range



Attending physician's mental notes

- The patient's high seizure threshold required additional pharmacological adjustment to standard ECT protocol
  - Anesthetic
    - Methohexital, a barbiturate, is the most commonly used anesthetic agent for ECT. It is characterized by fast emergence time; however, it is seizure-threshold neutral
    - Ketamine can lower seizure threshold, increase seizure duration, and lead to better-quality seizure compared to barbiturates
      - It was chosen initially over etomidate as it reduces transient cognitive dysfunction from ECT
    - Etomidate decreases seizure threshold and increases seizure duration
      - Acute hemodynamic response to ECT becomes more prominent
      - There is concern about adrenal function depression in long-term use
  - Caffeine IV
    - Caffeine was titrated to prolong seizure response during ECT
- Although patient is tolerating ECT, IV access issues need to be addressed for patient comfort and successful ECT treatments. The following strategy can be used to resolve this issue:
  - Local anesthetic agent could be used
  - More skilled personnel could assist in getting IV access
  - Veinviewer infrared scanner could be used to find deeper vein

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Although patient's increase in violence coincided with ECT tapering, other causes should be investigated to confirm the source of increased aggression
  - Measure clozapine and norclozapine levels to confirm medication compliance
  - Ophthalmology referral and surgery to reduce stress factor associated with decreased vision



Further investigation

- Is there an upper limit of how many ECT treatments can be given in one patient? When would you stop ECT treatment for this patient?
  - There is no upper limit to number of ECT treatments
  - As long as it is indicated and well tolerated, ECT can be continued



Case debrief

- Our patient has a long psychiatric history with diagnosis of schizophrenia and substance use disorder. He has an extensive psychotropic medication history including numerous failed trials of antipsychotic and other psychotropic medications
- Although he was on clozapine at the time of his initial visit, he was not at the maximum therapeutic dosage
- Even after maximum therapeutic level was reached, patient still suffered from CAH and violent behavior
- ECT trial led to a decrease in violent behavior



Take-home points

- Individuals with schizophrenia have a greater risk of engaging in violent behaviors
- Between 10% and 60% of patients with schizophrenia experience treatment resistance
- Clozapine is first-line therapy for TRS
- There is an association between schizophrenia and substance use disorder. The treatment team should evaluate whether aggressive behavior is a part of drug-seeking behavior
- Benzodiazepine does not play a role in anti-psychosis; therefore, it should be only used for acute agitation
- Antidepressants, anticonvulsants, mood stabilizers, and ECT can be used as adjunct therapy. However, ECT is preferred as it has highest rates of efficacy

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE



Performance in practice: confessions of a psychopharmacologist

What could have been done better to prevent deterioration of his symptoms?

- Early critical period in psychosis is important for secondary prevention of impairments and disabilities
- The patient received first dose of clozapine at the state forensic hospital 10 years after his initial diagnosis and psychiatric hospitalization. He may have benefited from an earlier clozapine trial

What could have been done in the outpatient setting to prevent relapses?

- Frequent bloodwork and follow-up to determine medical adherence. Routine drug screens to monitor substance use
- Adding long-acting antipsychotic medications (e.g., haloperidol) to increase compliance

What additional adjunct therapy can be used for this patient if symptoms relapse?

- Impulsivity is also associated with the risk of violence. Increasing cognitive capacities and reducing negative symptoms can help patients more adequately engage with psychotherapy to modulate impulsivity and violent behaviors
- Minocycline: double-blinded clinical study (n = 52) showed improvement in total symptoms, negative symptoms, and cognition with adjunct minocycline (100 mg po BID) compared to placebo
- Memantine: double-blinded clinical study (n = 52) showed improvement in total symptoms, negative symptoms, and composite memory score with adjunct memantine (titrated to 20 mg p.o. QD), compared to placebo
- Famotidine: double-blinded clinical study (n = 30) showed improvement in Positive and Negative Syndrome Scale (PANSS) with adjunct famotidine (titrated to 100 mg p.o. QD), compared to placebo



Tips and pearls

- It is important to gather prior medication history to understand the rationale behind dosage and medication changes to choose an appropriate treatment plan
- Psychiatrists should first try maximizing medicine as much as a patient tolerates, before considering medicine to be ineffective
- TRS definition – Kane Criteria
  - No relief ≥ 3 treatments, ≥ 6 weeks length, ≥ antipsychotics
  - Persistent poor functioning
  - Failure to respond to prospective high-dose first-generation antipsychotic (FGA) trial

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE

- Based on long-term studies, there is clozapine response in up to 60% of TRS, compared to < 5% with non-clozapine antipsychotics
- Clozapine can reduce violence, aggression, and substance abuse
- Clozapine receptor-mediated side effects
  - Sedation: caused by clozapine and norclozapine H1 antagonist activity
  - Hypersalivation:
    - Clozapine partial agonist in M1 and norclozapine's full agonist in M1
    - Clozapine's full antagonist in M3 and norclozapine's partial agonist at M3
    - Clozapine's impairment of swallowing reflex
  - Orthostatic hypotension and tachycardia: antimuscarinic activity
  - GI hypomotility / constipation:
    - Caused by clozapine and norclozapine activity on colonic M3 receptor
  - Weight gain
    - Due to increase in appetite mediated by clozapine H1 antagonism
  - Myoclonus and seizure
    - Possible explanation: D_2, H1, A1 receptor blockade
- Clozapine-induced myocarditis
  - Reported incidents vary from 0.06% to 3.88%, with mortality ranging from 10% to 30%
  - Highest risk within first month of therapy
  - Postulated to be caused by following: IgE-mediated hypersensitivity, inflammatory response from hypercatecholaminergic state, myocardial oxidative stress, reduced antioxidants, apoptosis
  - Management: withdrawal of drug, diuretics, angiotensin-converting enzyme (ACE) inhibitor, digoxin, beta-blocker
- Clozapine-induced neutropenia/agranulocytosis
  - 3% and 0.8% respectively, with the highest risk between 4 and 20 weeks; 85–90% of cases occur within 1 year
  - There are two proposed pathologic mechanisms: (1) immune-mediated response against haptenized neutrophil; (2) metabolite toxicity
  - Clinical presentation: fever, mouth ulcer, sore throat, but can be asymptomatic. Absolute neutrophil count less than 0.5×10^9/L
  - Management: weekly complete blood count (CBC) for the first 18 weeks, then every 2 weeks until week 52. Discontinue clozapine if agranulocytosis develops
- Smoking increases clozapine metabolism through induction of CYP1A2. This may explain possible discrepancies between reported medicine compliance and lab work

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

PATIENT FILE



Two-minute tutorial

- Violent behavior in schizophrenia
  - Patients with schizophrenia have increased risk of violent behavior that leads to arrest or conviction compared to the general population
- Clozapine is a first-line treatment for TRS
  - Severe adverse reactions include: myocarditis, seizure, and agranulocytosis
    - Assess clinical symptoms (flu-like symptoms) and laboratory results (CBC, clozapine/norclozapine level)
    - Management: discontinue clozapine. Depending on severity, it can be reinitiated at lower dose with close monitoring if benefit outweighs adverse reaction
  - Other side effects include: sedation, hypersalivation, orthostatic hypotension, gastrointestinal (GI) hypomobility, weight gain
    - Constipation may cause ileus and possible mortality. Laxative prophylaxis reduces this risk
- ECT adjunct therapy should be used if patient doesn't respond with optimal clozapine plasma level
  - On average, initial ECT trial consist of 6 to 12 treatments; usually performed two to three times a week for 2–4 weeks. There is no set number
  - Continue if patient tolerates well and has good clinical outcome
  - There is no maximum number of treatments
- ECT treatment can be adjusted with different pharmacological agents to be safe and effective, and help manage clinical complexities such as an elevated seizure threshold



Post-test question

Which of the following classes of medication should not be considered for long-term adjunct therapy for TRS?

A. Benzodiazepines
B. Mood stabilizers
C. Anticonvulsants
D. Electroconvulsive therapy (ECT)
E. Antidepressants

Answer: A

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

References

1. Birchwood, M., Todd, P., & Jackson, C. (1998). Early intervention in psychosis: the critical period hypothesis. *British Journal of Psychiatry: Supplement*, 172(33), 53–59.
2. Correll, C. U. & Howes, O. D. (2021). Treatment-resistant schizophrenia: definition, predictors, and therapy options. *Journal of Clinical Psychiatry*, 82(5). https://doi.org/10.4088/JCP.MY20096AH1C.
3. Correll, C. U., Yu, X., Xiang, Y., Kane, J. M., & Masand, P. (2017). Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. *Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists*, 29(2), 92–107.
4. Dold, M., Li, C., Gillies, D., & Leucht, S. (2013). Benzodiazepine augmentation of antipsychotic drugs in schizophrenia: a meta-analysis and Cochrane review of randomized controlled trials. *European Neuropsychopharmacology*, 23(9), 1023–1033. https://doi.org/10.1016/j.euroneuro.2013.03.001.
5. Espinoza, R. T. & Kellner, C. H. (2022). Electroconvulsive therapy. *New England Journal of Medicine*, 386(7), 667–672. https://doi.org/10.1056/NEJMra2034954.
6. Faay, M. D. M. & Sommer, I. E. (2021). Risk and prevention of aggression in patients with psychotic disorders. *American Journal of Psychiatry*, 178(3), 218–220. https://doi.org/10.1176/appi.ajp.2020.21010035.
7. Fazel, S., Gulati, G., Linsell, L., Geddes, J. R., & Grann, M. (2009). Schizophrenia and violence: systematic review and meta-analysis. *PLoS Medicine*, 6(8), e1000120. https://doi.org/10.1371/journal.pmed.1000120.
8. Higgins, J. M., San, C., Lagnado, G., Chua, D., & Mihic, T. (2019). Incidence and management of clozapine-induced myocarditis in a large tertiary hospital. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 64(8), 561–567. https://doi.org/10.1177/0706743718816058.
9. Hodgins, S., & Klein, S. (2017). New clinically relevant findings about violence by people with schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 62(2), 86–93. https://doi.org/10.1177/0706743716648300.
10. Hoptman, M. J. (2015). Impulsivity and aggression in schizophrenia: a neural circuitry perspective with implications for treatment. *CNS Spectrums*, 20(3), 280–286. https://doi.org/10.1017/S1092852915000206.

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

11. Hoyer, C., Kranaster, L., Janke, C., & Sartorius, A. (2014). Impact of the anesthetic agents ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. *European Archives of Psychiatry and Clinical Neuroscience*, 264(3), 255–261. https://doi.org/10.1007/s00406-013-0420-5.
12. Kane, J. (1988). Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45(9), 789. https://doi.org/10.1001/archpsyc.1988.01800330013001.
13. Kelly, D. L., Sullivan, K. M., McEvoy, J. P., et al. (2015). Adjunctive minocycline in clozapine-treated schizophrenia patients with persistent symptoms. *Journal of Clinical Psychopharmacology*, 35(4), 374–381. https://doi.org/10.1097/JCP.0000000000000345.
14. Khokhar, J. Y., Dwiel, L. L., Henricks, A. M., Doucette, W. T., & Green, A. I. (2018). The link between schizophrenia and substance use disorder: a unifying hypothesis. *Schizophrenia Research*, 194, 78–85. https://doi.org/10.1016/j.schres.2017.04.016.
15. McNiel, D. E., Eisner, J. P., & Binder, R. L. (2000). The relationship between command hallucinations and violence. *Psychiatric Services*, 51(10), 1288–1292. https://doi.org/10.1176/appi.ps.51.10.1288.
16. Meskanen, K., Ekelund, H., Laitinen, J., et al. (2013). A randomized clinical trial of histamine 2 receptor antagonism in treatment-resistant schizophrenia. *Journal of Clinical Psychopharmacology*, 33(4), 472–478. https://doi.org/10.1097/JCP.0b013e3182970490.
17. Mijovic, A. & MacCabe, J. H. (2020). Clozapine-induced agranulocytosis. *Annals of Hematology*, 99(11), 2477–2482. https://doi.org/10.1007/s00277-020-04215-y.
18. Mørup, M. F., Kymes, S. M., & Oudin Åström, D. (2020). A modelling approach to estimate the prevalence of treatment-resistant schizophrenia in the United States. *PloS One*, 15(6), e0234121. https://doi.org/10.1371/journal.pone.0234121.
19. Nucifora, F. C., Woznica, E., Lee, B. J., Cascella, N., & Sawa, A. (2019). Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. *Neurobiology of Disease*, 131, 104257. https://doi.org/10.1016/j.nbd.2018.08.016.
20. Schoretsanitis, G., Kane, J. M., Ruan, C.-J., Spina, E., Hiemke, C., & de Leon, J. (2019). A comprehensive review of the clinical utility of and a combined analysis of the clozapine/norclozapine ratio in therapeutic drug monitoring for adult patients. *Expert Review of Clinical Pharmacology*, 12(7), 603–621. https://doi.org/10.1080/17512433.2019.1617695.

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press

21. Sinclair, D. J. M., Zhao, S., Qi, F., Nyakyoma, K., Kwong, J. S. W., & Adams, C. E. (2019). Electroconvulsive therapy for treatment-resistant schizophrenia. *Schizophrenia Bulletin*, 45(4), 730–732. https://doi.org/10.1093/schbul/sbz037.
22. Stahl, S. M. (2011). Antipsychotic agents. In: *Stahl's Essential Psychopharmacology: Prescriber's Guide*, 4th ed. New York: Cambridge University Press, pp. 133–138.
23. Tiihonen, J., Suokas, J. T., Suvisaari, J. M., Haukka, J., & Korhonen, P. (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Archives of General Psychiatry*, 69(5), 476–483. https://doi.org/10.1001/archgenpsychiatry.2011.1532.
24. Veerman, S. R. T., Schulte, P. F. J., Smith, J. D., & de Haan, L. (2016). Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study. *Psychological Medicine*, 46(9), 1909–1921. https://doi.org/10.1017/S0033291716000398.

https://doi.org/10.1017/9781009335874.001 Published online by Cambridge University Press