SUPPLEMENTARY MATERIAL

A rational use of clozapine based on adverse drug reactions, pharmacokinetics and clinical pharmacopsychology

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Table S1. Current[a] recommendations for average clozapine maintenance doses. In the absence of TDM access, if the patient does not respond to the recommended average dose, add 50 mg/day extra. Do not use fluvoxamine without TDM[b]

C/D ratio	7	3.50	2.33	1.75	1.40	1.17	1.00	0.86	0.78	0.70	0.64	0.58	0.54	0.50	0.47	0.44	0.42	0.39
D	50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900
Asians (ancestral origin ranging from Pakistan to Japan and possibly the original inhabitants of the Americas)																		
			ns♀	s♀	ns♂	s♂												
Inhibitor[c]	ns♀	s♀	ns♂	s♂														
Obese[d]	ns♀	s♀	ns♂	s♂														
Inducers[e]						ns♀		s♀		ns♂		s♂						
US Caucasians[f] and African-Americans																		
						ns♀		s♀		ns♂		s♂						
Inhibitor[c]			ns♀	s♀	ns♂	s♂												
Obese[d]	ns♀	s♀	ns♂	s♂														
Inducers[e]									ns♀		s♀				ns♂			s♂[g]

C/D ratio, here refers to clozapine concentration-to-dose ratio measured in ng/ml per mg/day; D, dose in mg/day; ns, non-smoking; PM, poor metabolizer; s, smoking; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer, US, United States

[a]These dose recommendations based on linear pharmacokinetics will need to be updated as newly published TDM information becomes available. Make the clozapine administration as easy as possible, including rounding doses (600 mg/day may be easier than 575 mg/day) and administering twice a day (1/3 in the morning and 2/3 at night) or only at night, depending upon preference and ADRs.

[b]Studies show great variability; some provide a dose-correction factor of 0.10-0.20, which requires a clozapine dose 10 to 5 times lower. In Beijing Anding Hospital, fluvoxamine is no longer used because a clozapine patient died when co-prescribed fluvoxamine [65].

[c]Potent inhibitors such as oral contraceptives or high intake of caffeine may require a dose-correction factor of 0.5 [58, 59].

[d]In Asians our data is limited to outpatient samples with single TDM determinations in which patients with a high body mass index (around 30 and higher) behaved as clozapine PMs [46]. In US obese patients, we recommend TDM since we only have a statistical model [44] and Asian data [46].

[e]Potent inducers require a dose correction factor of 1.5-2.0. This dose estimation is a rough estimation and it is better to individualize the clozapine dose with TDM. Potent inducers are rifampicin, phenytoin, phenobarbital and carbamazepine (the package insert for some countries recommends against the co-prescription of carbamazepine due to its associations with agranulocytosis). There are no studies on high doses of oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day) but they may act as inducers. A case report suggested that topiramate can be a clinically relevant inducer [58].

[f]We are not ready to provide different dose recommendations for European Caucasians but an Italian outpatient study [45] and unpublished samples made available to the first author suggest that Europeans may need 200-400 mg/day versus 300-600 mg/day in US patients.

[g]On rare occasions, US s♂ with potent inducers or valproic acid are UMs and require clozapine doses >1000 mg/day to reach C>350 ng/ml [87]. We do not recommend prescribing doses >1000 mg/day without TDM.

Table S2. Current[a] recommended clozapine titrations for inpatients.[b] If any weekly CRP[c] is abnormal, hold dose escalation until CRP normalizes. Stop fluvoxamine, valproic acid, or oral contraceptives before titration.[d]

ASIANS

First week

Administer the first dose of 12.5 mg at night to avoid sedation and orthostatic hypotension.[e]
If tolerated, ↑ daily dose by 12.5 mg, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 50 mg/day at the end of the first week.

Second week

If tolerated,[e] ↑ twice 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 100 mg/day at the end of the second week.

Third week

If tolerated, [e] ↑ twice 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 150 mg/day at the end of the third week.

Fourth and following weeks

Recommended target dose is between 150 mg/day for a ♀ non-smoker and 300 mg/day for a ♂ smoker.
For ↑ dose: ↑ 25 mg/day each time with a target ↑ not >50 mg/week.
If TDM is available, measure clozapine level 1 week after reaching 150 mg/day to decide target dose.[g]

US CAUCASIANS AND AFRICAN-AMERICANS

First week

Administer the first dose of 25 mg at night to avoid sedation and orthostatic hypotension.[e]
If tolerated, ↑ daily dose by 25 mg, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 100 mg/day at the end of the first week.

Second week

If tolerated,[e] ↑ twice 50 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 200 mg/day at the end of the second week.

Third week

If tolerated,[e] ↑ twice 50 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[f]
Target 300 mg/day at the end of the third week.

Fourth and following weeks

Recommended target dose is between 300 mg/day for a ♀ non-smoker and 600 mg/day for a ♂ smoker.
For ↑dose: ↑ 50 mg/day each time with a target ↑ not >100 mg/week.
If TDM is available, measure clozapine level 1 week after reaching 300 mg/day to decide target dose.[h]

CRP, c-reactive protein; PM, poor metabolizer; UM, ultrarapid metabolizer; US, United States

[a]These recommendations will need to be updated as new information becomes available.

[b]We have no experience with outpatient titrations but, based on a recommendation from the Dutch guideline [223], it appears reasonable to ↓ titration in half. This means using Asian titration levels for US outpatients. It is very important for psychiatrists using outpatient titrations to be careful with ↑ dose and, when possible, supervise vital signs after the first few doses. Similarly, slower titrations are required in inpatients of geriatric age or who are taking medication that increases clozapine risk due to pharmacodynamic drug interactions. For them, consider the titration recommended for East Asians. When possible, stop benzodiazepines before starting clozapine since rare cases of collapse/respiratory arrest have been described, usually in the first 2 days of clozapine titration.

[c]We do not recommend starting clozapine until CRP is normal. If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine dose increases until CRP becomes normal.

[d]Fluvoxamine should be stopped before starting clozapine since it is an extremely powerful inhibitor and studies provide a dose-correction factor of 0.10-0.20. Oral contraceptives [58] or high intake of caffeine [59] may require a dose correction factor of 0.5. Valproic acid has been consistently associated with

myocarditis because at the beginning it can definitively behave as an inhibitor of clozapine metabolism. If there is no possibility of discontinuing oral contraceptives or valproic acid, we recommend ↓ the titration dose in half and use a target dose for maintenance, which is half the dose required for the patient's ethnicity, sex and smoking status (see Supplementary Table S1).

[e]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured. Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP levels and waiting until they normalize to proceed with titration.

[f]Avoid major dose ↑ during weekends or times with less nursing supervision.

[g]For an Asian patient with a dose=150 mg/day for 1 week, you measure clozapine concentration in the early morning before meds. Two examples are: a) the concentration=350 ng/ml; this provides a C/D ratio=350/150=2.4 and suggests the patient only needs a dose around 150 mg/day, or b) concentration =175 ng/ml; this provides a C/D ratio =175/150=1.2 and suggests the patient needs a dose ≥300 mg/day to reach a clozapine concentration = 350 ng/ml.

[h]For a US patient with dose =300 mg/day for 1 week, you measure clozapine concentration in the early morning before meds. Two examples are: a) the concentration =350 ng/ml; this provides a C/D ratio =350/300=1.2 and suggests the patient only needs a dose around 300 mg/day, or b) concentration =175 ng/ml; this provides a C/D ratio =175/300=0.6 and suggests the patient needs a dose ≥600 mg/day to reach a clozapine concentration = 350 ng/ml.

Supplementary Box S1. Clozapine history

Before 1975 [12]
• 1962: first human trial • 1967: Sandoz took over production. Clozapine was received with skepticism by clinicians. • Early 1970s: clozapine was marketed in some European countries • 1974: Clozapine was first tested in the US by Simpson and Varga [13].
From 1975 until US approval
• 1975: Clozapine-induced agranulocytosis was described in Finland [14]. • This led to a drop in development in the US and restrictions in many countries [12]. • 1977: Respiratory infections with fever increased theophylline half-life and concentration [15].[a] • 1980: the first case of clozapine-induced myocarditis from a clozapine overdose [16]
US approval and the 1990s
• 1988: US RCT: clozapine efficacious for treatment-refractory schizophrenia [17] • 1990: Clozapine was marketed in the US with a CPMS requiring weekly WBCs [12]. • 1993: Halve theophylline dose in respiratory infections [18]; due to CYP1A2 inhibition [19].[a] • 1994: Bertilsson et al. [20] described clozapine as mainly metabolized by CYP1A2. • 1995: Bandelow et al. [21]: first case of myocarditis from rapid clozapine titration by doctor.[b] • 1996: FDA: increase the requirements of pharmacokinetic studies in new drugs [22, 23].[c] Old drugs are not required to be studied (the US clozapine package insert is very deficient). • 1997: Two studies: Chinese had the same level with half the dose used in Caucasians [24, 25]. • 1999: Killian et al. [26] described 23 clozapine myocarditis from the Australia drug agency.
2000s
• 2000: Dejeveran et al. [27]: commented that all cases by Killian et al. were due to rapid titration. • 2001: Le Grenade et al. [28]: 28 myocarditis cases with 18 deaths in 10 years of FDA reports. • 2002: FDA approval for prevention of suicide in schizophrenia [29] and myocarditis warning box. First published case of elevations of clozapine levels during infection [30]. • 2003: Halving the dose during severe infections to avoid clozapine intoxication [31]. • 2005: The FDA approved criteria to reduce long-term WBC frequency in clozapine patients. • 2005: FDA: All SGAPs carry a warning of death by pneumonia in patients with dementia [32].[d] • 2007: The Australian guideline did not include the role of rapid titration in myocarditis [33].[e] Ghotbi et al. [34]: Koreans have lower caffeine clearance than Swedes.[f] • 2008: FDA: risk of 1) DDIs are due to CYP1A2, CYP2D6, and CYP3A4, and 2) CYP2D6 PMs.
2010s
• 2012: Cohen et al. [35]: incidence of clozapine-induced myocarditis of 7-34/1000 in Australia and of 0.07-0.6/1000 in other countries; Ronaldson et al. [36] established that rapid titration and valproate co-prescription were major predictors in an Australian case-control study.[g] • 2013: Kuo et al. [37]: clozapine is more clearly associated with pneumonia (Taiwan registry). • 2015: Ronaldson et al. [38] defended an incidence of 3% for clozapine myocarditis and the theory that countries other than Australia may be missing its diagnosis. Fredeuderich [39] and de Leon et al. [40] proposed there is a hypersensitive reaction associated with fast titration. US individual plans from the manufacturers are moved to REMS [41]. • 2018: In the Danish registry: In the first 2 months of 3,262 clozapine initiations: 0 myocarditis and 7 pneumonia cases [42]. Clark et al. [43] reviewed 40 cases of ↑ levels during infections. A statistical model proposed that severe obesity may significantly ↓ clozapine clearance [44]. • 2019: East Asians had lower clearance than Caucasians [45]. 7% of Asians are PMs [46]. • 2020: The package insert [47] needs to be changed: 1) Asians need lower doses than Caucasians [48]; 2) pneumonia has lethality risk [49], and 3) slow titration may prevent myocarditis [50].

Abbreviations: CPMS, Clozaril Patient Management System; CYP1A2, cytochrome P450 1A2; DDIs, drug-drug interactions; FDA, Food and Drug Administration; IV, intravenous; REMS, risk evaluation and mitigation strategy; US, United States; WBC, white blood cell count. Blue font is used to describe historical facts about two drugs, theophylline and caffeine, which are dependent on CYP1A2 for their metabolism and are important in understanding clozapine history.

[a]In the 1990s, it is established that the cytokines released during infections inhibit CYP1A2 and its expression [19]. As theophylline is mainly metabolized by CYP1A2, infections with fever increase serum theophylline concentrations and the IV dose needs to be corrected by 0.60, almost halved [18]. Therefore, it is not surprising that clozapine concentrations also increase with infections or with fever [31].

[b]They fail to stress the patient had an extremely rapid titration (500 mg/day on day 8).

[c]The FDA (Food and Drug Administration) discovered that ignoring pharmacokinetics and DDIs caused the death of 125 patients on terfenadine, which caused no deaths in RCTs [22]. The FDA started to progressively increase the requirements of pharmacokinetic studies of new drugs [23].

[d]It was unusual that clozapine was included in the package insert warning about "esophageal dysmotility and aspiration" for new SGAPs as a class [32]. Clozapine is rarely used in demented patients.

[e]The Guideline says, "Some groups have found that abnormalities are more likely to be associated with more rapid titration (Pantelis C, unpublished observations). There are, nevertheless, no current data or studies to definitively support this notion." Thus, the role of rapid titration was not included in the consensus guideline [33].

[f]Caffeine can be used as a probe of CYP1A2 activity. After controlling for confounders including sex, smoking, oral contraceptives and CYP1A2 alleles, the CYP1A2 activity of Koreans (East Asians) is 0.65 lower than in Swedes (Caucasians). Therefore, it is not surprising that Asians have lower clozapine clearance than Caucasians [34].

[g]If one considers that valproate can be an inhibitor of clozapine metabolism, one can assume that co-prescription with valproate is equivalent to experiencing rapid titration even when standard titration is used.

Supplementary Box S2. Personalizing clozapine dosing

1. Effects of sex and smoking on clozapine metabolism
• Sex. ♂ tend to have 0.84 of the ♀ C/D ratio [45]. Estrogens inhibit clozapine metabolism. • Smoking. Smokers tend to have 0.81 of the non-smokers' C/D ratio [45]. Tobacco smoke has PAHs which induce CYP1A2. Smoking 1 pack/day may lead to maximum induction [52].
2. Effects of Asian ethnicity on clozapine C/D ratios
• US. C/D ratios typically range from 0.6 for ♂ smokers to 1.2 for ♀ non-smokers [53]. • Asian[a] C/D ratios typically range from 1.2 for ♂ smokers to 2.4 for ♀ non-smokers [46].
3. Genetics of clozapine metabolism
• CYP1A2 genotyping is not ready for clinical use [54]. • PMs. Two rare CYP1A2 alleles (*6 and *7) with no or little activity have been described [54]. Around 3% of European Caucasians [45] and 7% of Asians may be PMs [46] within their group. • UMs. Most published cases can be explained by lack of adherence or by inducers [54].
4. Inducers
• Roasted coffee beans. PAHs (such as those in tobacco smoke) can be found in Indian coffee [46]. • Potent inducers. Rifampicin, carbamazepine, phenytoin or phenobarbital: ↑ D by 1.5-2 times [55]. • Mild inducers. Omeprazole and modafanil [56] are mild CYP1A2 inducers. High Ds of oxcarbazepine (≥1200 mg/day) or topiramate (≥400 mg/day) may be inducers [55]. • Valproic acid in some patients can induce norclozapine metabolism [57].
5. Inhibitors
• Fluvoxamine: ↓ D to 1/5 to 1/10 to keep same C. Do not use in the absence of TDM [55]. • Ciprofloxacin and norfloxacin should not be prescribed; they are powerful CYP1A2 inhibitors. • Oral contraceptives: ↓ to 1/2 of the prior D to keep the same C [58]. • Caffeine.[b] A high amount of caffeine can behave as a competitive inhibitor [59]. • Other SSRIs. Paroxetine and fluoxetine can be ignored in most patients [55]. Sertraline in high Ds can occasionally cause ↑ clozapine Cs [60]. • TCAs have the potential to be competitive inhibitors [55]. • Perphenazine in high Ds [61] and flupenthixol may also inhibit clozapine metabolism [62]. • Valproic acid in some patients inhibit the metabolism of clozapine, the parent compound [57].
6. Renal excretion
• Gemfibrozil inhibited norclozapine clearance by inhibiting a renal transporter [63]. • Geriatric age is associated with ↓ clozapine clearance [64] by ↓ norclozapine renal elimination.
7. Obesity
• Using a model in a US RCT, weight gain may become clinically relevant in extreme obesity [44]. The PM status of 4 Asians (0.7% of 586) was explained by obesity [46].
8. Inflammation
• In 131 Chinese inpatients with 18 episodes of infection in 16 patients which contaminated 2% of days (482/24,789), we found: 1) no clinically relevant effects in the 11% of infection episodes which presented with no leukocytosis or ↑ CRP, 2) ↓ D to 1/2 would be advisable in 61% of the infection episodes, and 3) ↓ D to 1/3 would be advisable in 28% of infection episodes [65]. • Clozapine-induced inflammation can happen during titration and can manifest as CRP elevations, fever and/or myocarditis, but other rarer forms have been described [66].
10. Pregnancy
• CYP1A2 activity ↓ during the second and third trimesters [67], possibly ↑ clozapine Cs.

C, concentrations; C/D, concentration-to-dose; CRP, c-reactive protein; CYP1A2, cytochrome P450 1A2; D, dose; PAH, polycyclic aromatic hydrocarbon; PM, poor metabolizer; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer; US, United States

[a]Asians are defined as those whose ancestral origins range geographically from Pakistan to Japan [48]. Natives of the Americas are also descendants of Asians.

[b]Caffeine is present in coffee, tea and caffeinated beverages. A detailed list of estimated caffeine content in US beverages is provided on a webpage https://www.caffeineinformer.com/the-caffeine-database

No study provides clear instructions to clinicians on what quantity of caffeine could be clinically relevant. Until prospective studies are available, we recommend caution with increases or decreases of daily caffeine intake of > 1 cup of coffee (or 2 cans of caffeinated soda) in non-smokers and > 3 cups of coffee (or 6 cans of caffeinated soda) in smokers. For example, when a smoker taking clozapine increases caffeine intake by 3 cups of coffee (e.g., from 2 to 5 cups per day), clinicians should watch for increased side effects due to ↑ clozapine C [5].

Supplementary Box S3. CLO TDM

1. Measuring CLO TDM
• Half-life varies in individual patients according to clearance (longer in PMs and shorter in UMs). Single-dose studies provide short half-lives and suggest dosing twice a day [70]. CLO is lipophilic [71,72]. In repeated Ds, CLO deposits in fat tissue providing longer half-lives [73]: 17-34 hours in 3 patients [74]. This may explain why CLO can be administered once a day. • Trough. Serum Cs vary during the day and standardized Cs are measured when at their lowest value or valley (trough Cs) before the next CLO D. Early in the morning is a reasonable time.[a] • Steady-state.[b] Pharmacokinetic textbooks usually state that 5 half-lives provide approximately 95% of steady-state concentrations and 7 half-lives provide 99% of them [75]. On the other hand, TDM articles usually simplify the guideline by proposing that 5 half-lives are required before reaching steady state. A clinician needs to remember to wait at least 5 days from a CLO C change to order CLO TDM, but it is better to wait at least a week.
2. C/D ratio
• Serum CLO and NORC Cs are usually measured by laboratories in ng/ml. The ratio, calculated by dividing the trough steady-state plasma C of CLO by the daily D of CLO, is called the CLO C/D ratio (ng/ml per mg/day), which is a measure of CLO clearance. • In 1994, Jerling et al. [76] demonstrated that an inducer decreases CLO C/D ratio while an inhibitor increases it. When comparing individuals, a very low CLO C/D ratio indicates a UM (assuming compliance) while a very high C/D ratio indicates a CLO PM. As CLO follows linear kinetics, the CLO C/D ratio is a constant in an individual unless something changes the clearance, such as the addition of an inducer or inhibitor. • Total CLO C/D ratio is calculated by dividing the total C (CLO C + NORC C) by the CLO D and is a better measure of the clearance than the CLO C/D ratio. CLO has antipsychotic efficacy, while NCLO does not. The total CLO C/D ratio may be better than the CLO C/D ratio as a measure of predicting the ADR risk [68].
3. Therapeutic reference range in schizophrenia
• Expert guideline [51]: serum CLO C therapeutic reference range is 350-600 ng/mL [77-83].[c]
4. Therapeutic index is 1.7 (600/350=1.7)
• According to the FDA, it can be calculated by dividing the upper reference range by the lower reference range [84, 85]. Although it is not a formal definition, the FDA considers <2 a narrow therapeutic index [85]. CLO has the narrowest of therapeutic indexes among second-generation antipsychotics; therefore, it may be the most prone to cause D-dependent ADRs [55].
5. Laboratory alert level
• The expert consensus guideline proposes that 1000 ng/mL be defined as a CLO laboratory alert level that obliges the laboratory to provide feedback immediately to the prescribing physician [51]. This CLO alert C has not been well studied. In the absence of clozapine ADRs, it is reasonable to repeat the CLO TDM when it is > 1000 ng/ml and consider ↓ the D [69]. • The total C (CLO C + NCLO C) may better reflect what are usually called D-related ADRs such as seizures, hypersalivation and constipation. These D-related ADRs may be more closely related to total CLO Cs than to Ds since, in an individual patient, resolving ADRs requires reducing both CLO and NCLO C to avoid these ADRs [68].
6. Long-term monitoring of inpatients used to develop these recommendations
• Smoking changes [58, 79, 86] • Co-prescription of inducers and inhibitors [58-61, 63, 87] • Obesity [44] • Inflammation [31, 50, 65, 88-90] • Discontinuation [74, 91]

ADRs, adverse drug reactions; C, concentration; C/D, concentration-to-dose; CLO, clozapine; D, dose; NCLO, norclozapine; PM, poor metabolizer; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer

[a]In patients taking their only dose at night, the trough C will be at night before the D but it is not practical to measure at that time; thus, it is reasonable to measure C early in the morning and still consider it a trough C.

[b]Once steady state has been reached there is equilibrium between the drug's absorption and elimination.

[c]The AGNP therapeutic range is based on 7 studies [77-83]. Most of them did not describe the administration pattern. A carefully designed inpatient trial [82] with administration over 2-3 days reported efficacy of the 200-300 ng/ml dose and the 350-450 ng/ml dose, with no advantage for 350-450 ng/ml over 200-300 ng/ml. Thus, in inpatients with the daily dose divided into 2-3 administrations/day, it is possible that lower Cs (200-300 ng/ml) may be enough.

Supplementary Box S4. Baseline risk of poor outcomes from TRS without treatment

1. Decreased life expectancy in schizophrenia
• In a meta-analysis [112], schizophrenia was associated with a weighted average of 14.5 years of potential life lost (CI, 11.2-17.8), but the specific contribution of TRS, although substantial, is not known. • In a Swedish cohort with >20,000 patients, the cumulative antipsychotic exposure displays a U-shaped curve for overall mortality [113]: o first-episode patients with no antipsychotic use: HR = 9.9 (5.9-16.6) o no antipsychotic exposure: HR = 6.3 (CI 5.5-7.3) o high exposure group: HR = 5.7 (CI 5.2-6.2) o low exposure group: HR = 4.1 (3.6–4.6) o moderate exposure group: HR = 4.0 (3.7–4.4).
2. Clozapine increases life expectancy compared with no antipsychotics or other antipsychotics
• In a meta-analysis of 24 studies with long-term follow-up of treatment, Vermeulen et al. [114] found long-term, crude mortality rate ratios were: o lower when treated with clozapine (mortality rate ratio = 0.56, CI = 0.36-0.85, p=0.007) o higher when patients were treated with other antipsychotics • In a Finnish 20-year study of >62,000 patients [115], the cumulative mortality rates during maximum follow-up of 20 years were: o 46% with no antipsychotic use o 26% with the use of any antipsychotic o 16% with clozapine use. The most beneficial mortality outcomes were: in terms of all causes, adjusted HR=0.39 (CI: 0.36-0.43); cardiovascular-adjusted, HR=0.55 (CI: 0.47-0.64); and suicide mortality, adjusted HR=0.21 (CI: 0.15-0.29). • In a more recent British cohort of >2000, Cho et al. [116] found that the protective effect of clozapine on all-cause mortality was significant: adjusted HR 0.61 (CI: 0.38-0.97; p=0.04).

CI, 95% confidence interval; HR, hazard ratio; SMD, standardized mean differences; TRS, treatment-resistant schizophrenia

Supplementary Box S5. Responsiveness to clozapine in TRS: efficacy, effectiveness and well-being

1. EFFICACY: RCTs AND META-ANALYSES

- In a 2016 meta-analysis, Siskind et al. [121] found 21 studies with a clozapine NNT=9. Afterwards, they calculated a response rate for clozapine of 40% (CI 36.8-43.4%) [61].
- In two network meta-analyses of the same research group:
  - In acute RCTs for multiple-episode schizophrenia, Huhn et al. [123] found clozapine provided the largest effect size estimates measured by SMD=-0·89 (CI -1·08 to -0·71).
  - In TRS: Samara et al. found [122] a pattern of superiority for olanzapine, clozapine, and risperidone, but clozapine was not significantly better than most other drugs. This article has been widely criticized due to study heterogeneity [124], lack of representativeness [107] and lack of attention to other behaviors including aggression [125].

2. EFFECTIVENESS: COHORT STUDIES

- In 22 observational studies in 2017, Land et al. [127] found that clozapine significantly ↓ the proportion of people hospitalized compared to controls: RR = 0.74 (CI 0.69-0.80, P < 0.001).
- In 63 cohort studies in 2020, Masuda et al. [128] found clozapine was significantly associated with:
  - lower hospitalization risk (N=19)[a]: RR=0.82 (CI 0.73-0.92; P = .001; NNT=18; CI, 12-40), and
  - all-cause discontinuation (N=16):[a] RR=0.73 (CI 0.64-0.84; P < .001; NNT=8; CI 6-12).

  Clozapine was also significantly associated with better outcomes regarding:
  - overall symptoms (N=10):[a] SMD=-0.302 (CI, -0.572 to -0.032; P = .03), and
  - Clinical Global Impression scale severity (N=4):[a] SMD=-1.182(CI, -2.243 to -0.122; P = .03).

3. WELL-BEING

3.1. Better profile related to causing EPS

- In 1987, Van Putten and Marder [130] described the behavioral toxicity of antipsychotics with:
  - akinesia associated with a subjective sense of sedation and excessive sleeping
  - akathisia strongly associated with depression and dysphoric responses.
- This has been ignored until recently [131, 132].
- In a 2013 meta-analysis of 15 antipsychotics compared with placebo [133]:
  - clozapine was the only one with an OR lower than 1: OR=0.3, (CI 0.12 to 0.62)
- Clozapine can cause EPS; its beneficial effects tend to be greater than its negative effects [134].
- Antipsychotics cause more EPS as their dose is ↑; it does not happen with clozapine [135].
- Clozapine produces little akathisia [136] and frequently is beneficial for patients with chronic akathisia [137] who usually report major improvements in well-being.
- Clozapine rarely causes TD [138], but is a good treatment for TD according to recent systematic reviews [139, 140] and for tardive dystonia [141]. Some patients report an increase in well-being when clozapine ↓ their TD and ↓ associated social embarrassment, a neglected issue in TD [142].

3.2. Better profile for treating hostility

- A meta-analysis of the use of antipsychotics in schizophrenia spectrum disorders demonstrated that clozapine showed moderate effect size with low heterogeneity in hostility when compared with first-generation antipsychotics [143].
- Moreover, clozapine is a very well-regarded drug for treating hostility in TRS and other patients in forensic facilities [144]. These patients are ignored by RCTs due to the extreme risks.

3.3. The awakening phenomenon

- A not well-studied phenomenon is that when, clozapine was approved for TRS in many long-term hospitals in the USA and Europe, some patients who had been very ill for many years had a completely unexpected response that changed their lives completely and was compared to the "awakening" [145-147] described by Oliver Sacks after the introduction of L-dopa to patients with post-encephalitic parkinsonism.

CI, 95% confidence interval; EPS, extrapyramidal symptoms; NNT, number needed to treat; RCT, randomized clinical trial; RR, relative risk; SMD, standardized mean differences; TD, tardive dyskinesia; TRS, treatment-resistant schizophrenia

[a]Not all 63 cohort studies had data for all statistical analyses. The N indicates the number of studies used for that specific statistical analysis.

Supplementary Box S6. An update on clozapine-induced agranulocytosis

1. Mechanism
• The clozapine-induced agranulocytosis mechanism is not well understood but it is believed that, in these patients, antibodies are developed against the neutrophils [151].
2. Timing
• The peak incidence occurs at one month of exposure and declines to negligible levels after one year of treatment [152].
3. Prevalence and lethality
• A recent meta-analysis provided a prevalence of agranulocytosis of 0.4% (CI 0.3-0.6%); deaths caused by agranulocytosis were 0.05% (CI 0.03-0.09%) [153]. • VigiBase is the World Health Organization database that receives reports on ADRs. o Reports come from 134 drug agencies in countries all over the world. o Since its start in 1968, it currently has >20 million reports of spontaneously reported ADRs. o On July 15, 2019, from 144,020 clozapine reports, 1/3 of the reports (33%, 47,879/144,020) were from agranulocytosis-related ADRs. These numbers include cases from before WBC monitoring was required. o After eliminating duplicates, there were 34,931 reports with a relative lethality of 2% (550/34,931) [49].
4. Risk factors
• In the US, the risk factors are Caucasian race, age between 40 and 59 years, and male sex [151], which are not specific enough to be helpful. • Genetic studies suggest that some HLA alleles [154] may be important, but currently there is not enough knowledge to identify patients at high risk; a commercial test using HLA was introduced in 2008 in the US and then withdrawn from the market [155].

CI, 95% confidence interval; HLA, human leukocyte antigen; WBC, white blood cell

Supplementary Box S7. Pathophysiology of pneumonia in clozapine patients

1. The possible role of TRS

- The association between clozapine and pneumonia may be partly explained by the greater severity of illness in clozapine patients, who are frequently the most TRS patients and have relatively high rates of smoking. Therefore, the contributing effects of the severity level of mental illness on pneumonia needs to be further explored by future studies in clozapine patients.
- In a study in the Danish registry [157], clozapine appears to have specific effects independent of the greater severity of illness in clozapine patients, since using a mirror-image design:
  - 1.87% (35/1872) had pneumonia in the first year of clozapine use.
  - 1.22% (23/1872) had pneumonia in the year before clozapine use.
  - This is an increase of 0.64% (12/1872) (P=0.10).
- In the same study, patients with TRS (future clozapine candidates) may have greater pneumonia risk:
  - 1.22% (23/1872) in future clozapine candidates
  - 0.70% (101/14484) in antipsychotic-naïve patients after excluding clozapine patients
  - This is an increase of 0.52%.

2. Clozapine can increase the risk of infections

- During the rare occurrence of agranulocytosis, there is ↑ risk of infection.
- In the absence of neutropenia, studies have associated clozapine with ↑ infection risk.
  - ↑ tuberculosis: Canadian cases [163] and Taiwan registry [164]: aRR=1.63 (CI: 1.10-2.40; P = 0.014).
  - ↑ antibiotic use: retrospective chart review in a Canadian hospital [165], and Danish registry [166] RR=1.43 (CI: 1.26-1.61, P<0.0001).
- British case-control study comparing patients treated with clozapine and patients treated with other antipsychotics [167]:
  - ↑ number of patients with low levels of IgG (OR = 6.00, CI 1.31-27.44); IgA (OR = 16.75, CI 2.18-128.60); and IgM (OR = 3.26, CI 1.75-6.08).
  - > 5 courses of antibiotics in the prior year: 5.3% (5/123) clozapine versus 1% (1/111) other.
- In vitro study [168], clozapine immunosuppressant effects: ↑ interleukin-1 receptor antagonist.

3. Clozapine can contribute to aspiration pneumonia

- As with all antipsychotics, clozapine can interfere with swallowing, as it ↑ the potential for aspiration [169].
- The potential for aspiration and aspiration pneumonia during antipsychotic treatment may be further increased by sedation and hypersalivation. As clozapine is more prone to cause sedation and hypersalivation than other antipsychotics, it is not surprising that clozapine may be more strongly associated with aspiration pneumonia [169].

4. Pneumonia can complicate other serious clozapine ADRs

- On rare occasions, severe CIGH or myocarditis can be complicated by pneumonia [169].

5. Clozapine intoxication during pneumonia

- Once pneumonia develops, clozapine co-prescription may be particularly lethal and worse than other antipsychotics. Severe inflammation during pneumonia releases cytokines that inhibit CYP1A2 expression and/or activity and ↑ serum clozapine concentrations.
- In smokers, smoking cessation can also contribute to ↑ serum clozapine concentrations.
- The risk of concentration-related ADRs including hypersalivation, sedation, aspiration or even arrhythmia, creating very dangerous positive feedback, is further increased [169].

ADR, adverse drug reaction; aRR, adjusted risk ratio; CI, 95% confidence interval; CIGH, clozapine-induced gastrointestinal hypomotility; Ig, immunoglobulin; RR, relative risk; TRS, treatment-resistant schizophrenia

Supplementary Box S8. Recommendations regarding pneumonia in clozapine patients [162]

1. Prevention
• Education. The clozapine prescriber should educate his/her outpatients and families to be attentive to signs or symptoms of infection/inflammation or fever and to contact them immediately to prevent clozapine intoxication. • Measuring baseline clozapine TDM and clozapine C/D ratio. After reaching a stable maintenance clozapine D, the prescriber may measure two or three trough serum Cs and calculate their clozapine C/D ratios at steady state. By calculating the mean of the baseline clozapine C/D ratios, the clinician can establish a baseline for clozapine metabolism in that patient and the lowest clozapine D, providing a therapeutic serum C. In the unfortunate event that the patient develops pneumonia, this baseline clozapine C/D ratio can be compared with the decreased clozapine C/D ratio during the pneumonia. • Decrease risk of sedation and/or hypersalivation. Clozapine administration should be moved to the most convenient times in order to increase adherence and decrease these ADRs. Hypersalivation should be treated with non-pharmacological interventions, and preferably with local antimuscarinic treatments which may have less risk of increasing the risk of constipation than oral anticholinergic drugs, such as benztropine, or biperiden [170, 171]. Discontinuation of other co-medications associated with sedation should be considered. As benzodiazepines are associated with sedation, swallowing disturbances and pneumonia, clinicians may need to consider ↓ or discontinuing them to ↓ the risk of aspiration pneumonia. • Pneumonia vaccines. Although there are no studies, it may be reasonable to give pneumonia vaccines to clozapine patients to ↓ risk of pneumonia not associated with aspiration, but the vaccines may not be as effective due to clozapine effects on immunological mechanisms.
2. During the infection
• CRP and clozapine TDM. Once an infection has developed, the prescriber should order a CRP level immediately. If possible, a trough clozapine TDM should be measured. • Monitoring for clozapine intoxication and considering halving the clozapine D. When fever and/or CRP elevations develop, the prescriber should consider immediately halving the clozapine D and monitor for signs of clozapine intoxication. • When access to baseline clozapine TDM and TDM during pneumonia is available. A D correction factor can be calculated by dividing the baseline clozapine C/D ratio by the clozapine C/D ratio during pneumonia. In our study of infections [65], in ¼ of patients it is better to use a D correction factor of 1/3 (↓ D to 1/3) to maintain the same clozapine Cs as before the pneumonia. • Signs of clozapine intoxication. If signs of clozapine intoxication are already present, it may be safer to stop clozapine for 2-3 days or until the clozapine TDM report arrives. The decision to discontinue clozapine needs to be individualized and include careful consideration of risk and benefits. Different countries have different rules about restarting clozapine after discontinuation that need to be considered regarding the decision to discontinue clozapine completely or maintain a very low D (25 mg/day). • Antibiotics. Strong CYP1A2 inhibitors (ciprofloxacin or norfloxacin) should not be used.
3. After the infection
• After the inflammation has resolved and the CRP is normal, observe the individual response to first ↑ D. Moving from a half D during infection to a baseline clozapine D after infection may be possible with little or no uptitration (these Ds provide roughly the same Cs). • If the clinician did not measure a baseline clozapine C/D ratio before the infection, it may be wise to obtain clozapine C/D ratios for several weeks after the infection to establish the lowest clozapine D providing therapeutic serum C and efficacy for maintenance treatment with the fewest ADRs in order to avoid the recurrence of pneumonia in the future.

ADR, adverse drug reaction; C, concentration; C/D, concentration-to-dose; CRP, c-reactive protein; D, dose.

Supplementary Box S9. Pathophysiology of clozapine-induced myocarditis

1. Lamotrigine-induced Stevens-Johnson syndrome as a model

- 1991 UK approval [174]. Rapid dose escalations were associated with a skin rash that could lead to Stevens-Johnson syndrome/toxic epidermal necrolysis [175, 176].
- 1994 modification of titration: ↓ incidence of Stevens-Johnson syndrome.
  The 3 patterns of titration started with:
  - a half dose in patients taking the inhibitor valproate,
  - a normal dose in patients not taking inhibitors or inducers, and
  - twice the dose in patients taking inducers [175, 176].
- Pathophysiological model. Two phases:
  - The first sign that the titration is too fast for that patient is usually a skin rash.
  - Uptitration continues and auto-antibodies and Stevens-Johnson syndrome develop [177].
- Peculiar ADR. It appears to be immunological, but it is not idiosyncratic, since it is related to a titration that is too fast for that specific patient. Moreover, it can be prevented and avoided by avoiding an elevation in serum concentration of lamotrigine that is too fast for that specific patient.

2. Pathophysiology of clozapine-induced myocarditis in this model

- Pathophysiological model. Three phases [162]:
  - First, a clozapine titration that is too fast leads to CRP elevations and/or fever.
  - Second, cytokine release ↓ clozapine metabolism (a positive feedback mechanism).
  - Third, if the clozapine uptitration continues, the inflammation evolves into myocarditis, probably with the development of auto-antibodies.
- The same physiopathology applies to all clozapine-induced inflammations during rapid titration [66]:
  - Other inflammations, such as clozapine-induced pericarditis
  - Clozapine-induced fever or ↑ CRP, which are early signs

3. Prevention of clozapine-induced myocarditis based on this model

- Slow and personalized titrations: See Table S2. No way exists to a priori identify clozapine genetic PMs.
- Our experience with CRP:
  - Baseline: We do not recommend starting clozapine until CRP is normal.
  - Weekly for 6 weeks or until maintenance dose is reached: If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine dose increases until CRP becomes normal.
  - This is a cheap and easy alternative to extensive monitoring recommended by Australian experts [38, 178, 179].
- Our experience with troponine:
  - It always becomes abnormal after CRP has been abnormal.
  - We do not recommend using weekly troponine as a standard test for countries with fewer resources, since it will be more expensive. CRP is more easily available and more sensitive.

ADR, adverse drug reaction; CRP, c-reactive protein; PM, poor metabolizer; UK, United Kingdom

Supplementary Box S10. Clozapine-induced myocarditis and rapid titration

1. Critical review of the literature on the role of rapid titrations (Supplementary Box S1)

- 1980: first clozapine-induced myocarditis: rapid titration in a patient during an overdose [16].
- 1995: the first case with no overdose was published [21]: the first rapid titration by a doctor.
- 2000: Dejeveran et al. [27] commented that the Australian review by Killian et al. [26] that brought attention to clozapine-induced myocarditis neglected to comment that all these Australian cases were associated with rapid titration.
- 2007: Australian experts writing a clozapine guideline ignored the observation of one of them, Petridis, that myocarditis was associated with rapid titration [33].
- 2012: Ronaldson et al. [36], in an Australian case-control study, described rapid titration and co-prescription with valproic acid as risk factors for clozapine-induced myocarditis.

2. Ignoring clozapine PMs makes normal titration too rapid for specific patients

- CLO PMs need to be identified within two major genetic groups [48, 180]:[a]
  - Asians (ancestral origins ranging from Pakistan to Japan) and possibly Native Americans [48]
  - Non-Asians: Caucasians and people of African ancestry
- Also consider the effects of sex and smoking [45, 46].
- In the phenomenon of phenoconversion, normal metabolizers can become PMs due to [54]:
  - co-prescription of inhibitors such as fluvoxamine, oral contraceptives or valproic acid
  - obesity
  - undiagnosed inflammation
- Some clozapine PMs appear **NOT** to suffer from phenoconversion (possibly genetic PMs):
  - Asians: around 7% (range 3.8-12.9%) [69]
  - European Caucasians: <3% [45].

3. Recently published data supporting this model

- In the US: 5 cases of clozapine-induced myocarditis were reinterpreted by us due to [50]:
  - 4 with rapid titration
  - 1 possibly genetic PM who could not tolerate a clozapine dose of 25 mg/day
- In Australia and possibly Canada [181, 182] a 3% incidence may be explained by:
  - using Caucasian-level titration in Asians or
  - using normal titration in non-Asian patients who are taking valproic acid.
- Oral contraceptives (inhibitors)[b] lead to high risk of clozapine-induced inflammation [58].

4. Recommendations for starting clozapine in patients on valproic acid

- Published data:
  - Valproic acid is a frequent medication in many patients started on clozapine. This is not surprising since it is used for epilepsy and aggressive behaviors.
  - Valproic acid is a risk factor for clozapine-induced myocarditis in articles from Australia [36], Canada [181], the US [183, 184], Turkey [185], Poland [186] and Japan [187].
- Experience of the first author:
  - In the hospital of the first author, there have been 4 cases of clozapine-induced myocarditis since 2002. One of them appeared to be a genetic PM and the other 3 were on valproic acid. In 2 of them TDM suggested that they behave as clozapine PMs. In summary, for some of the patients valproic acid appears to be an inhibitor.
  - In some other patients, valproic acid appears to be an inducer [87].
- Current clozapine titration recommendation for patients on valproic acid:
  - Avoid using it if possible
  - If needed, use extremely slow clozapine titration to avoid myocarditis.
  - Use clozapine TDM in case valproic acid serves as an inducer.

ADR, adverse drug reaction; PM, poor metabolizer; TDM, therapeutic drug monitoring
[a]These two groups are a simplification. People from Western Asia comprise a variety of genetic backgrounds [180]. Currently, there is no data on how this influences clozapine metabolism.
[b]The literature describes 4 cases of women taking oral contraceptives [58]. All 4 of them appear to behave as clozapine PMs. For 2 of them there was information on titration (normal titration for Caucasians led to a clozapine-induced fever in one and clozapine-induced pericarditis in the other case).

Supplementary Box S11. Other potentially lethal clozapine-ADRs

1. Constipation

- Complications are referred to as clozapine-induced gastro-intestinal hypomotility (CIGH) [188].
- The FDA strengthened the warning about the risk of hospitalization and even death [189].
- Our Vigibase search: CIGH produced 12% of the fatal outcomes (326/2,814) [49].
- A study in New Zealand estimated a mortality rate of 7 patients/10,000 clozapine users [190].
- Clozapine is more prone to cause constipation than other antipsychotics. Up to 1/3 of clozapine patients may have it [191], but controlled treatment studies are limited [192].
- Our recommendations. Until better studies exist, the following is reasonable [188, 192, 193]:
  - Use proper hydration, physical exercise and food high in fiber.
  - Use a preventive laxative prescription in every clozapine patient.
  - Use the lowest clozapine dose.
  - When possible, avoid systemic use of antimuscarinic drugs to treat hypersalivation.

2. Arrhythmia

- Our Vigibase search: 5% of the fatal outcomes (319/6,927) [49].
- Published data:
  - In vitro study: clozapine can blockade heart potassium repolarizing channels [195]
  - Clinical cases: occasionally associated clozapine with QTc prolongations [196].
  - Most clinical studies: clozapine effects on QTc may not be clinically relevant [197, 198]
  - A pharmacoepidemiology study: clozapine is associated with sudden deaths [199].
- Our recommendation: the same as for other second-generation antipsychotics [200]:
  Torsades de pointes is very rare, but is more frequent in females aged > 65 years.
  Clinicians need to consider that additive risk factors are:
  - family history of sudden death
  - personal history of syncope
  - arrhythmias or heart conditions
  - hypokalemia or hypomagnesemia
  - co-prescription of other medications that ↑ QTc
- Clinicians should use the lowest clozapine D providing efficacy in each specific patient.

3. Seizures

- Our Vigibase search: 5% of the fatal outcomes (308/6,231) [49].
- Reviews suggest that clozapine may be the worst among the antipsychotics for ↓ the seizure threshold, while the mechanisms behind this effect are not well understood [201].
- In 5,629 US clozapine patients, Pacia and Devinsky [202] found prevalences of 1.3% (71/5,629) of generalized tonic-clonic seizures, with two types of seizures happening during:
  - the titration phase: at low Ds (< 300 mg/day) (history of seizures or epilepsy), and
  - the maintenance phase: at high Ds ≥ 600 mg/day.
- As with other dose-related ADRs, clozapine-induced seizures are serum C-related, they appear to be better predicted by the total serum C (clozapine + norclozapine) [68, 203].
- Our recommendation [201, 204-206]:
  - For prevention, use the lowest clozapine D providing efficacy in each specific patient.
  - After a seizure, consider ↓ clozapine D before considering adding an AED.
  - Lamotrigine has the best pharmacokinetic and pharmacodynamic profiles among AEDs.
  - Valproic acid can be an inhibitor and an inducer; use clozapine TDM.

4. Syncope

- In our Vigibase search, syncope had 7% of the fatal outcomes (299/4,058) [49]
- Syncope usually occurs during early titration. The best way of avoiding it is monitoring orthostatic changes during titration [207] and providing personalized titration.

ADR, adverse drug reaction; AED, antiepileptic drug; C, concentration; CIGH, clozapine-induced gastrointestinal hypomotility; D, dose

Supplementary Box S12. Current clozapine use

1. Main barriers according to a narrative review by Farooq et al. [219]:

- Mandatory blood testing
- Fear of serious ADRs and lack of adherence by the patients
- Difficulty in identifying suitable patients
- Service fragmentation
- Inadequate training in or exposure to using clozapine

They proposed a certification requiring competence in initiating and managing clozapine ADRs.

2. Main solutions according to a systematic review by Verdoux et al. [220]:

- Implementation of integrated clozapine clinics
- Simplification of blood monitoring
- Education for prescribers and contact with experienced prescribers

They also stressed that unequal access to clozapine care should be more systematically handled by mental health facilities and health regulatory agencies.

3. Other practical barriers

- Pharmacies. Knowles et al. [221] stressed that in some countries increasing access may be facilitated by increasing clozapine access in community pharmacies.
- Inpatient initiation. A barrier somewhat specific to the US, where there is great fear of litigation. Many psychiatrists such as those in the first author's state expect clozapine to be initiated in a hospital and do not want to risk outpatient initiation as is the norm in other countries. According to a survey among clinicians in the UK, inpatient initiation is the third most important barrier after concerns over blood monitoring and ADRs [222].

4. Success in ↑ clozapine use

- In the Netherlands, a group of experts developed a clozapine guideline that encourages outpatient initiation [223] and which has been extremely successful in increasing clozapine prescription. Two important aspects of this Dutch experience that can be imitated in other countries:
  - The guideline is used in teaching residents.
  - The board members who developed the guideline are available to clinicians for consultation [224].
- New Zealand is another country with success in increasing clozapine prescription [224]. In community mental health centers in an area of New Zealand during 2000-2004, clozapine ↑ from 21% to 33% of antipsychotic prescriptions [225]. This was associated with higher rates of regular occupational activity (37% vs. 14%) and lower rates of compulsory treatment (25% vs. 46%) and significantly lower hospitalization rates (mean = 0.6 vs. mean = 3.1). Moreover, after 4 years, 93% of clozapine patients were still being prescribed clozapine [225].

ADR, adverse drug reaction; UK, United Kingdom; US, United States

Supplementary Box S13. Technological advances coming to the market

1. Pharmacogenetic tests

- Commercial tests. Multiple commercial pharmacogenetic tests in psychiatry have been introduced in several countries [229] and many include recommendations on clozapine. The tests have been introduced with almost no regulatory supervision and limited or no data on analytic validity, clinical validity and clinical utility [230, 231]. These commercial tests have limited agreement among themselves in their recommendations [232].
- HLA alleles. The commercial test using HLA introduced in 2008 in the US was withdrawn from the market [155]. Currently there is not enough knowledge of the associated HLA alleles for its use in clinical practice.
- Predicting efficacy. The commercial test using receptor pharmacodynamic genes introduced in the United Kingdom is no longer available [155]. Small studies with no replications have found some genes to be associated with clozapine efficacy [233]. Currently, there is not enough knowledge for their use in clinical practice.
- CYP1A2 gene. Known CYP1A2 alleles are not helpful for clozapine dosing [234]. In the future, unknown CYP1A2 mutations probably will identify clozapine PMs in different ethnicities [54].

2. Point of care for measuring WBC

- Athelas One. It uses venous blood or capillary collection. Blood is collected into the Athelas test strips and is analyzed using computer vision technology. A smartphone or tablet is required to initiate the test and view test results [235].
- HemoCue WBC DIFF. It measures total WBC and differential counts in capillary or venous whole blood using a finger prick method. Bui et al. [236] recommended repeating the measurement with a venous sample when WBC is in the lower reference range.
- Chempaq XBC. It measures hemoglobin, WBCs, and a 3-part differential using a finger stick method [235].

3. Advances in clozapine TDM

- Point of care. Saladax has adapted immunoassay technology to detect clozapine and other antipsychotics [235]. An electrochemical system is also being developed [237].
- DBS. Specimens are collected by applying a few drops of blood, drawn by pricking from the finger or other areas, onto specially manufactured absorbent filter paper and sent for analysis.
    - Geers et al. [238] studied the validity of clozapine DBS in the clinical environment in samples from the Netherlands and Russia. They reported as potential problems the potentially confounding effects of blood spot volume and the effects of the hematocrit.
    - In Japan, Nakahara et al. [239] developed another DBS method with a simplified version on a disk, which they propose is suitable for self-collection.
    - Temesi et al. [240] reported that, when using DBS, N-clozapine-oxide reverts to clozapine.
    - Future studies will need to establish whether or not: 1) DBS provides reliable results for personalizing clozapine dosing by using clozapine C/D ratios and 2) it can be widely used across different countries at a relatively affordable cost.
- Long-term adherence. Man et al. [241] describes development of a nomogram for the estimation of long-term adherence to clozapine therapy using neutrophil fluorescence. Currently, it is not clear what the clinical value of this method may be.

C/D, concentration-to-dose; CYP1A2, cytochrome P450 1A2; DBS, dried blood spot; FDA: Food and Drug Administration; HLA, human leukocyte antigen; TDM, therapeutic drug monitoring; WBC, white blood cell count

Supplementary Box S14. Clozapine indications

Approvals
• Clozapine is approved in the US by the FDA in monotherapy for TRS. • In other Western countries, clozapine is also approved for TRS [148], but the indications in Asian countries vary substantially [242]. • In the US, clozapine was also approved for suicide risk in schizophrenia in 2002 [29].
Other indications that would be off-label in the US:
• augmentation treatment after partial response to clozapine in TRS with co-prescription with other drugs [243, 244] or ECT [245, 246],[a] • acute schizophrenia in adults [247], • treatment resistance after the first psychotic episode [248], • schizophrenia in adolescents and children [249], • schizophrenia with aggressive behavior [250], or self-harm [251], • schizophrenia with comorbid substance abuse [252], • tardive dyskinesia [139, 140] and tardive dystonia [141], • treatment-resistant bipolar disorder [253], • polydipsia associated with severe mental illness [254], • aggression in patients with intellectual disability which does not respond to other treatments [207, 255], • severe self-aggressive behavior in borderline personality disorder [256], or • psychosis in Parkinson's disease [257]

ECT, electroconvulsive therapy; FDA, Food and Drug Administration; TRS, treatment-resistant schizophrenia; US, United States

[a]The studies using drug augmentation have not systematically ruled out pharmacokinetic effects from increasing clozapine concentrations [244]. The limited information that we have on ECT augmentation suggests that it is not mediated by increases in clozapine concentrations [246].