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Titrating clozapine amidst recommendations proposing high myocarditis risk and rapid titrations

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Running title: Clozapine titration

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Ronaldson and Fitzgerald (1) propose that many cases of clozapine-induced myocarditis are overlooked and the actual worldwide incidence in clozapine patients is around 3%, which is in conflict with published evidence. This extraordinarily high estimation was calculated by averaging rates of 1.1% and 5.0% from two Australian studies with 122 and 124 clozapine patients, respectively. After reviewing the literature in English, Cohen et al. (2) estimated the incidence of clozapine-induced myocarditis to be 0.07 – 0.6 per 1000 in non-Australian countries. In China, clozapine is widely prescribed. Until very recently, clozapine was a first-line antipsychotic prescribed in 25-60% of schizophrenia patients and in many patients with severe mood disorders (3). A 2015 search of the literature in Chinese reveals that clozapine-induced myocarditis has been extremely rarely reported.

If the 3% incidence is correct, pharmacoepidemiological studies should demonstrate that thousands of non-Australian clozapine patients are dying every year but they suggest the opposite; clozapine may prevent cardiovascular deaths compared to other antipsychotics. In an 11-year follow-up mortality study in 66,000 Finnish schizophrenia patients, clozapine showed the lowest mortality with an adjusted hazard ratio (HR) of 0.74 (95% confidence interval, CI 0.60-0.91). In a 5-year follow-up of almost 7,000 Finnish patients with first-onset schizophrenia, clozapine showed an adjusted odds ratio (OR) for cardiovascular death of 0.23 (CI, 0.05-1.02). In a schizophrenia cohort study of 26,000 Swedish patients, clozapine showed an adjusted OR for all deaths of 0.92 (CI 0.70-1.22). In a 3-year study of a cohort of 67,000 patients from the US Clozapine National Registry, there was no death attributed to myocarditis and less than 10 deaths attributed to two cardiac categories: 1) acute myocardial infarction and 2) conduction disorders or sudden death. In a 6-10 year follow-up of a cohort of 1000 clozapine patients in Maryland (USA), cardiac deaths were 35% (32/92) of clozapine deaths and the adjusted standardized mortality rates for cardiovascular mortality were comparable to risperidone deaths. In a 5-year follow-up of a cohort from London (UK) including 14,000 patients with serious mental illness, clozapine was associated with lower mortality (adjusted HR=0.4; CI 0.2–0.7).

We believe that it is not correct to extrapolate these unusual incidences from two Australian studies totaling less than 300 patients titrated on clozapine to the thousands of patients titrated worldwide. Rapid clozapine dose titration has been suggested as an explanation for the risk of myocarditis by a 2012 Australian article titled "Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study". Rapid titration may be one of the key factors contributing to the very high rates of clozapine-induced myocarditis in Australia. This is supported by an ongoing Venezuelan prospective clozapine study, by one of us, following 59 patients longitudinally. Most of them were started at low doses (< 100 mg/day) and given slow titrations. The only subject with suspected myocarditis (reported chest discomfort, positive troponine I and ST segment abnormalities at day 7 of clozapine administration) was a 30-year-old male started on clozapine at the high dose of 200 mg/day.

We suggest that instead of raising unfounded clinical concerns for non-Australians, Australian prescribers should consider adopting slower titrating schedules, as a prior lamotrigine pharmacology story tells us. Lamotrigine-induced Stevens-Johnson is another idiosyncratic adverse drug reaction (ADR) associated with rapid titrations. It was radically reduced when the manufacturers recommended a slow titration in their prescribing information (or package insert), specifying the need of an even lower initial dose and slower titration in patients taking valproate, an inhibitor of lamotrigine's metabolism. Slow clozapine titration strategies, including a slower pace for patients taking clozapine inhibitors, should be studied as a strategy for preventing myocarditis in Australia.

At the other extreme from Ronaldson et al. (1), Ifteni et al. (4) extrapolated from a small sample, recommending rapid titration as safe. They studied 38 Romanian clozapine-naïve patients with schizophrenia who were prescribed an average clozapine dose of 156 mg/day on the first day, with a range of 25 to 400 mg/day, and an average maximum dose of 409 mg/day on average at day 7. We recommend against this type of rapid titration in clozapine-naïve patients unless they are very closely monitored in research settings.

To an inexperienced clinician already concerned about clozapine ADR risk and the practical difficulties of starting new patients on clozapine, it would seem quite confusing and possible intimidating after reading these articles written by us, the so-called clozapine experts. Is further confusing or intimidating clinicians concerning clozapine utilization a problem? Yes, it is a major problem. Meta-analyses unquestionably demonstrate that clozapine is the most effective of all antipsychotics, but authors from many countries, except China, argue that clozapine is severely underutilized in spite of its documented efficacy for treatment-refractory schizophrenia or schizophrenia-associated suicidality. Elaborating on the benefits of clozapine's off-label uses would require a longer article.

Regarding Ifteni et al.'s proposal of rapid titration in clozapine-naïve patients (4), we recommend very slow clozapine titration with careful monitoring in a Dutch guideline mainly developed for outpatients (http://www.clozapinepluswerkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf, accessed on 25 February 2015) and in a pharmacokinetic guideline for inpatients (5). The Dutch guideline recommends initial doses of 6.25 or 12.5 mg, doubling the dose the second day, and then 25-50 mg/day increases, but no more than 300 mg/day for the first 14 days. The pharmacokinetic guideline recommends starting with 25 mg (12.5 mg in patients expected to have slower clozapine metabolism), increasing by 25 (12.5) mg/day in the first week, and then by 50 (25) mg/day reaching 100 (50) mg/day at the end of the first week, 200 (100) mg/day at the end of the second week, and 300 (150) mg/day at the end of the third week. Both guidelines insist on slower titrations after abnormalities in orthostatic changes of blood pressure and pulse, or sedation and initial doses at night.

Our conclusion, for those who revere the "science" of evidence-based medicine, is that if it is correct that in non-Australian countries clozapine-induced myocarditis has an incidence <1%, then an evidence-based approach will not work with this rare frequency because gathering the evidence would require support from the deep pockets of pharmaceutical companies that can afford to fund studies of thousands of patients. No pharmaceutical company is going to support intensive studies to establish or rule out clozapine-induced myocarditis as an idiosyncratic ADR probably associated with rapid titration.

Our take-home message for clinicians includes the hope that they will forgive us, the clozapine experts, for our inconsistent messages on the speed with which clozapine can safely be titrated. For our part, we think that we should refrain from making any more comments based on extrapolations from small to very small studies. Although there are more than 10,000 clozapine articles in PubMed, but this is not enough for definitive evidence-based recommendations for clozapine titration on a worldwide basis. In the midst of this large number of articles, some data ignored by non-Chinese clozapine researchers supports the hypothesis that clozapine metabolism and dosing may be different in those with Chinese ancestry, which is presumably explained by a pharmacogenetic difference (5). If confirmed true that the Chinese do indeed need lower clozapine doses and, presumably, slower titration, this may also be relevant in preventing clozapine-induced myocarditis in Chinese people, possibly in other East Asians, and Caucasians who are CYP2C19 poor metabolizers (5). If this pharmacogenetic- and ethnic-based dosing difference has not been definitively established, imagine how limited the clozapine evidence-based literature is. Unfortunately, as Naylor declared, “Clinical medicine seems to consist of a few things we know, a few things we think we know (but probably don’t), and lots of things we don’t know at all.” In the context of limited evidence, we should err on the side of recommending safety without inducing more clozapine phobia and encourage a trial of clozapine with slow titration in all patients with treatment-resistant schizophrenia.

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