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Commentary

Clozapine-induced Gastrointestinal Hypomotility — New Objective Evidence for an Underestimated Side-effect☆

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Clozapine is still the most effective antipsychotic drug in the management of treatment-resistant schizophrenia and alternative strategies are currently not foreseeable. Clinicians are aware of the typical and frequent clozapine side-effects such as hypotension, sedation, tachycardia and sialorrhea as well as the rare but nevertheless life-threatening complications like agranulocytosis or myocarditis. However, clozapine-induced constipation with the consecutive risk for ileus still receives little attention, which is a matter of concern: (1) constipation linked to antipsychotic treatment is generally underestimated (De Hert et al., 2011a) and (2) clozapine seems to be specifically associated with high-grade constipation, intestinal obstruction and paralytic ileus (De Fazio et al., 2015; Palmer et al., 2008; De Hert et al., 2011b). International guidelines address antipsychotic-induced constipation (Hasan et al., 2012) and provide evidence-based pharmacological and non-pharmacological treatment recommendations based on a sparse database (Hasan et al., 2013). To fill the clinician's knowledge gap, new evidence regarding antipsychotic-induced constipation and the relationship to certain compounds is needed.

Every-Palmer et al. (2016) provide a novel and important study to shed more light on this relationship. They used for the very first time a standardized radiopaque marker method (multiple radiopaque marker (ROM) bolus technique) to measure colonic transit times (CTTs) of patients receiving antipsychotics as well as comparing the effects of clozapine and non-clozapine antipsychotic agents on CCT. This approach is new for clinical psychiatry and allows for a reliable and objective measure of CCT with limited burden for the patients. Their work is of particular significance, as it (1) reveals for the first time increased CTTs in nearly all patients receiving clozapine (but surprisingly not in non-clozapine treated patients), (2) that this is associated with the clozapine serum levels and (3) that this hypomotility was not reported by patients by the means of subjective constipation symptoms. Remarkably, CTTs in clozapine were four times longer than for other antipsychotics or population norms and 4 of 5 clozapine-treated patients showed clear hypomotility (Every-Palmer et al., 2016). Therefore, the work of Every-Palmer et al. (2016) will force clinical psychiatrists in future to think about new strategies to assess clozapine-induced gastrointestinal hypomotility in terms of using objective measures rather than counting solely on the patients' subjective complaints. The disparity between subjective symptoms and objective measures of prolonged CTTs is discussed in the paper of Every-Palmer et al. (2016) as a multifactorial effect of reduced pain sensitivity and the difficulty to communicate discomfort of schizophrenia patients, as well as the sedative component of clozapine in general. Other publications discuss the presence of negative symptoms, the social isolation of patients, the unhealthy lifestyle with low physical activity and limited fluid intake, but also physicians lacking awareness, as reasons why somatic comorbidities, like constipation, are not detected in schizophrenia patients (De Hert et al., 2011b). This study highlights the fact that gastrointestinal hypomotility should be expected in a magnitude of patients treated with clozapine and that objective measures might be needed to detect this side-effect before severe complications appear. Surprisingly, patients receiving other, so called non-clozapine antipsychotics, showed in the work of Every-Palmer et al. (2016) transit times within the normal range contrasting clinical experience and previous data indicating an increased risk for constipation following the treatment with various antipsychotics (De Hert et al., 2011b). The reason for this discrepancy remains unclear and further research is needed to disentangle the complex interplay between CTTs and constipation in patients treated with non-clozapine antipsychotics. More research is also necessary to evaluate the predictive value of increased CTT and severe treatment complications in schizophrenia patients.

For clinical psychiatry, this new data confirms the need for an active and systematic screening and monitoring of constipations symptoms (De Hert et al., 2011b). This includes also the need to use objective measures (including radiology and ultrasound) as well as the use of diaries to access defecation frequency and the importance of physical examinations to detect abdominal pathology in patients receiving antipsychotics. Saying this, one should bear in mind that antipsychotics are not exclusively used in schizophrenia patients (although clozapine is mainly confined to schizophrenia), but also in nearly all other

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psychiatric conditions which makes clear that the issue of increased CTT and gastrointestinal hypomotility is of general importance in psychiatry. Interestingly, the authors also reported a positive correlation between serum clozapine levels and longer transit times. Treatment guidelines recommend high clozapine-levels ≥ 350 ng/ml (Hasan et al., 2012; Buchanan et al., 2010) in treatment-resistant schizophrenia and these presented findings demonstrate that we need to pay special attention to gastrointestinal complications in those patients who are at risk for an unfavorable clinical course. Moreover, the issue of a potential indication extension of clozapine as a last resort antipsychotic in terms of its earlier application is under discussion (Remington et al., 2013) and a recently published retrospective cohort study underlined the superior effectiveness of clozapine with regard to the time to hospitalization and the risk for treatment discontinuation (Stroup et al., 2016). Therefore, it might be reasonably assumed that clozapine will remain one of the most important antipsychotics and prescription rates may even increase.

Considering the work of Every-Palmer et al. (2016), we need to focus our attention on gastrointestinal hypomotility and consider specific interventions. While the authors recommend prophylactic laxative treatment based on evidence from the use of long-term opioids, schizophrenia treatment guidelines pronounce the efficacy of lifestyle modulations and nutrition advice (Hasan et al., 2013). However, if the underlying problem is mainly gut dysmotility as indicated by the discussed paper (Every-Palmer et al., 2016), the aforementioned intervention could be inadequate to treat this significant treatment side-effect. Further research is needed to evaluate evidence-based treatment recommendation and prevention strategies for antipsychotic-induced constipation. Although the paper by Every-Palmer et al. (2016) demonstrates a discrepancy between objective measures of gastrointestinal hypomotility and subjective symptom presentation, we should not forget, independent of such high-quality findings, that barriers to somatic monitoring and treatment are one of the major causes of excess mortality in schizophrenia patients (De Hert et al., 2011b).

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