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Glasgow Antipsychotic Side-effects Scale for Clozapine — Development and validation of a clozapine-specific side-effects scale

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ABSTRACT

Objective: The authors developed and validated a clozapine-specific side-effects scale capable of eliciting the subjectively unpleasant side-effects of clozapine.
Methods: Questions from the original Glasgow Antipsychotic Side-effects Scale (GASS) were compared to a list of the most commonly reported clozapine side-effects and those with a significant subjective burden were included in the GASS for Clozapine (GASS-C). The original authors of the GASS and a group of mental health professionals from the UK and Ireland were enlisted to comment on the questions in the GASS-C based on their clinical experience. 110 clozapine outpatients from two sites completed the GASS-C, the original GASS and a repeat GASS-C. Statistical analyses were performed using SPSS for Windows version 19.
Results: The GASS-C was shown to have construct validity, in that Spearman's correlation coefficient was 0.816 ($p < 0.001$) with the original GASS, whilst Cohen's kappa coefficient was >0.77 ($p < 0.001$) for one question and >0.81 ($p < 0.001$) for remaining relevant questions. GASS-C was also shown to have strong test–retest reliability, in that Cronbach's alpha coefficient was >0.907 ($p < 0.001$), whilst Cohen's kappa coefficient was >0.81 ($p < 0.001$) for 12 questions and >0.61 ($p < 0.001$) for the remaining four questions.
Conclusion: The GASS-C is a valid and reliable clinical tool to enable a systematic assessment of the subjectively unpleasant side-effects of clozapine. Future research should focus on how the scale can be utilised as a clinical tool to improve real-world outcomes such as adherence to clozapine therapy and quality of life.

1. Introduction

For people with schizophrenia whose illness has not responded adequately to prior antipsychotic treatment, only clozapine has demonstrated greater efficacy compared with first and other second generation antipsychotics (Lewis et al., 2006; McEvoy et al., 2006). However, clozapine's pharmacological profile has the potential to produce a wide range of subjectively unpleasant side-effects, many of which are benign (Williams and Purvis, 2012), whilst some are potentially more serious. The most commonly reported subjectively unpleasant side-effects of clozapine (both according to the manufacturers and anecdotally) include daytime drowsiness/sedation, dizziness/postural hypotension, tachycardia, myoclonus, hypersalivation, anticholinergic effects including dry mouth and blurred vision, nausea, vomiting, gastric reflux/heartburn, constipation, nocturnal enuresis, polyuria, polydipsia, weight gain and sexual dysfunction (Clozaril 100 mg tablets, Novartis Ireland Limited, 2013; BNF: British National Formulary, 66, 2013). Monitoring protocols have been implemented to manage clozapine's potentially life-threatening haematological side-effects, as well as serious but often 'silent' cardiac and metabolic side-effects (Hodge and Jespersen, 2009). However, certain subjectively unpleasant side-effects including some with potentially serious consequences are not subject to systematic monitoring. The most prominent omission is that of constipation,

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which is reported in 14–60% of clozapine users (Palmer et al., 2008), with many more reported fatalities from gastrointestinal complications than from blood dyscrasias (Bleakley and Taylor, 2013).

1.1. Subjectively unpleasant side-effects of clozapine

The subjectively unpleasant side-effects of clozapine can be inconvenient and, in certain circumstances, extremely embarrassing (Hodge and Jespersen, 2009). They can cause stigma, impact negatively on patients' self-esteem and medication adherence (leading to an increased relapse rate) and reduce quality of life (Hodge and Jespersen, 2009; Haddad and Sharma, 2007). Although second generation antipsychotics like clozapine have a lower liability for extrapyramidal side-effects (EPSEs), side-effects such as sedation, hypersalivation, sexual dysfunction, weight gain and anticholinergic side-effects can be equally (if not more) disabling (Yusufi et al., 2007). Additionally, the common assumption that clozapine's side-effects are more common in the early stages of treatment and that tolerance usually develops has been challenged in 2007 by Yusufi and colleagues who found that 75% of patients on maintenance clozapine therapy reported at least one moderate or severe side-effect (Yusufi et al., 2007) (Table 1).

1.2. Why a clozapine-specific side-effects scale?

For several reasons, none of the side-effects scales listed is ideal for clinical use to assess potential side-effects of clozapine. Firstly, all were designed as generic scales to assess antipsychotic side-effects in general and not specifically those of clozapine. Whilst markedly different degrees of risk exist between second generation antipsychotics for a number of side-effects (Haddad and Sharma, 2007), clozapine differs more significantly in a number of respects than other antipsychotics in its class (Asenjo Lobos et al., 2010). Both the ANNSERS and the SRA-34 are lengthy instruments containing 48 and 34 questions respectively. The ANNSERS is clinician-rated, requiring training prior to administration which is not ideal in clinical practice where time is likely to be at a premium. The SRA-34 does not enquire about a number of side-effects associated with clozapine such as tachycardia, myoclonus, dry mouth, gastric reflux/heartburn and nocturnal enuresis. Whilst the GASS and SMARTS both have the advantage of being self-report and short, there are certain side-effects that are more likely to occur with clozapine (for example hypersalivation and gastric reflux/heartburn) that are not specifically listed by either scale. In addition, the GASS does not enquire about constipation which, as previously stated, can have life-threatening consequences if left untreated (Palmer et al., 2008) and both scales contain questions about side-effects unrelated to clozapine such as hyperprolactinaemia (Clozaril 100 mg tablets, Novartis Ireland Limited, 2013). Given that clozapine is the only antipsychotic with proven efficacy in the treatment of refractory schizophrenia (Lewis et al., 2006; McEvoy et al., 2006), the development of a clozapine-specific side-effects scale that is easy to use in routine clinical practice may help optimise patient outcomes.

2. Method

2.1. Ethical approval

The Saint John of God Hospitaller Ministries Ethics Committee and the Aston University Ethics Committee granted ethical approval for the study.

2.2. Constructing the scale

The first version of the GASS for Clozapine (GASS-C) was developed by comparing all 22 questions from the original GASS to a list of the most commonly reported clozapine side-effects from the manufacturers' summary of product characteristics (Clozaril 100 mg tablets, Novartis Ireland Limited, 2013) and the British National Formulary (BNF: British National Formulary, 66, 2013). Those side-effects with a significant subjective burden that cannot be easily measured objectively were considered for inclusion in the GASS-C. The original authors of the GASS along with other mental health professionals from London and Manchester were invited to make suggestions and recommendations on the questions in the GASS-C based on their clinical experience and their feedback incorporated into the scale.

The GASS-C (see Appendix 1) contains 16 questions, comprising nine original GASS questions (one of which has been split in two), four adapted originals and two new questions. Nine questions from the original GASS not specifically relevant to clozapine therapy were removed.

The scale also contains a section on smoking and a question about whether smoking habit has recently increased or decreased. Alterations in smoking habit can have a large effect (average +/− 50%) on dose requirement and smoking cessation is associated with a rapid increase (i.e., over 2–4 days) in plasma clozapine concentration with consequent risk of toxicity (Flanagan R.J., 2008). Additionally, there is a section on caffeine intake as the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period (Clozaril 100 mg tablets, Novartis Ireland Limited 2013).

2.3. Study setting

The study was based in the clozapine clinics provided by two adjacent mental health service providers, the first a private psychiatric hospital and the second a community mental health service.

2.4. Participants and study procedures

The inclusion criteria were individuals aged between 18 and 65 who were attending either clinic for blood monitoring and medication collection between October 2013 and February 2014. The exclusion criteria included current inpatient status, and pregnancy. All eligible individuals who were attending either clinic were invited to participate. After complete description of the study to the participants, written informed consent was obtained. On receipt of the signed consent form, participants were invited to complete the GASS-C the GASS and the GASS-C for a

Table 1
Summary of existing antipsychotic side-effects scales.

Scale	Description
Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS)	48-item clinician rated scale that aims to comprehensively rate the full range of non-neurological adverse drug reactions commonly seen across the spectrum of first and second generation antipsychotic drugs (Ohlsen et al., 2008)
Glasgow Antipsychotic Side-effects Scale (GASS)	22 question self-rating scale for detecting second generation antipsychotic side-effects, validated in a community population against the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Waddell and Taylor, 2008)
Systematic Monitoring of Adverse events Related to Treatments (SMARTS)	Patient completed 11 item checklist with an additional open 12th question that enquires about any other possible side-effects (Haddad et al., 2014a,b)
Subjects' Response to Antipsychotics questionnaire (SRA-34)	Measures a combination of relevant self-reported desired therapeutic and undesired adverse effects of antipsychotic medication including second generation drugs (Lako et al., 2013).