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SHORT COMMUNICATION

An observational study of clozapine induced sedation and its pharmacological management

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Abstract
Clozapine induced sedation is common but its management is unclear. We analyzed the factors associated with clozapine-induced sedation and the efficacy of common pharmacological strategies. We conducted a naturalistic observational study using two years electronic records of a cohort patients and three analyses: a cross sectional analysis of factors associated with total number of hours slept (as an objective proxy of sedation), and two prospective analyses of which factors were associated with changes in hours slept and the efficacy of two pharmacological strategies. 133 patients were included, of which 64.7% slept at least 9 h daily. Among monotherapy patients (n=30), only norclozapine levels (r=.367, p=.03) correlated with hours slept.
Using the prospective cohort (n=107), 42 patients decreased the number of hours slept, due to decreasing clozapine (40%) or augmenting with aripiprazole (36%). These two strategies were recommended to 22 (20.6%) and 23 (21.5%) subjects respectively but the majority (81.8% and 73.9%) did not reduce number of hours slept. Thus, pharmacological and non-pharmacological factors are involved in sedation.
Norclozapine plasma levels correlated with total sleeping hours. Reducing clozapine and aripiprazole augmentation were associated to amelioration of sedation, although both strategies were effective only in a limited numbers of subjects.

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1. Introduction

Clozapine is the only approved medication for treatment of resistant schizophrenia (TRS) due to its superior efficacy (Leucht et al., 2013). Clozapine underuse (only prescribed for 5% of eligible patients (Moore et al., 2007)) is mainly due to its side effects which reduce initial prescription (Nielsen et al., 2013) and cause discontinuation. There are clear protocols for managing some side effects (i.e. agranulocytosis), but others like sedation remains a challenge for clinicians (Nielsen et al., 2013).

The mechanism of clozapine's sedation is still unclear although sedation may have a dose-dependent effect. A study found correlations at high clozapine plasma concentrations above 0.35 mg/l. (Yusufi et al., 2007), but the evidence is still inconclusive for lower levels (Flanagan, 2008; Young et al., 1998). Clozapine's hepatic metabolism has substantial inter-individual variability due to genetic and environmental variables that influence CYP enzymes (Khan and Preskorn, 2005), such as dose, gender, smoking, age, body weight, caffeine intake, drug–drug interactions (Rostami-Hodjegan et al., 2004).

Dose dependent histaminergic receptor 1 (H1) antagonism is considered as the main cause of sedation (Lameh et al., 2007). If so, the differential receptor profile of clozapine and its metabolites may influence sedation. Norclozapine, clozapine's main metabolite, has a 20-50-fold lower affinity over H1, a 5-fold lower affinity to α1-adrenoceptors and a 10-fold higher affinity to δ-opioid receptors compared to clozapine (Lameh et al., 2007). Norclozapine is a muscarinic receptor partial agonist, while clozapine function as antagonist. Norclozapine plasma levels have been reported also to influence sedation (Légaré et al., 2013) but results from in vivo and vitro studies are inconclusive.

Besides plasma levels, other factors have been associated with sedation, including age (Bishara and Taylor, 2014), concomitant medications, total clozapine dose, night time dose (Young et al., 1998) and the clozapine:norclozapine plasma ratio (Légaré et al., 2013), although a definitive answer is still unclear.

Most patients tolerate sedation within 6 weeks of initiation (Marinkovic et al., 1994), but for those 17–67% permanently affected (Safferman et al., 1991) management is unclear. Recommendation is to reduce dose or a single evening dose (Taylor et al., 2015). When clozapine reduction is not an option there is no clear consensus for proceeding. Adding aripirazole (Barbui et al., 2011), or fluvoxamine as a metabolic inhibitor to decrease total dose and increase clozapine:norclozapine ratio (Légaré et al., 2013) have been reported as effective, but there is poor replication of this evidence (Lammers et al., 1999; Young et al., 1998). Using stimulants (dextroamphetamine or others) has been proposed, but increases the risk of psychotic exacerbation (Young et al., 1998).

1.1. Aims

Additionally, the study of clozapine-induced sedation is limited by several factors, including the lack of a clear concept definition and how to measure it. Sedation is frequently measured as a categorical variable, despite being mostly a subjective assessment of patients experience, that may include excess of daytime sleepiness or increased hours of night sleep (Brown et al., 2005). Most of the literature about sedation has been provided by randomized clinical trials, but external validity and recommendations are limited due to the strict inclusion criteria. Observational naturalistic studies overcome this limitation, as exclusion criteria are set to the minimum to favor the generalization of results (Black, 1996).

We focused on answering three research questions: 1) what are the factors associated with the number of hours of sleep in clozapine-treated patients? 2) what are the factors associated with changes in the hours slept? and 3) how efficient are these strategies for decreasing sleeping hours? We used the clinical evaluations from clozapine clinics cohorts, analyzing which factors were cross-sectionally associated with the number of hours slept, as a proxy for sedation, and the efficacy of common pharmacological strategies using a prospective analysis.

2. Experimental procedures

2.1. Design

Naturalistic observational analysis of the number of hours slept and the changes over time in clozapine treated patients using two years records from an electronic clinical database.

2.2. Setting

Cambridgeshire and Peterborough NHS Foundation Trust cover 800,000 habitants. Three clinics serve to 450 clozapine patients who are reviewed at least annually. All interviews follow a structured assessment (described below).

2.3. Electronic records

The Clinical and Research Database (CRD) is an ethically approved electronic database (13/EE/0121) to store and analyze clinical data from the Clinic users during all medical consultations. Extracted data maintains patient anonymity.

2.4. Clinical assessments

Assessments included the review of prescribed medication (types, doses), current smoking habits (cigarettes/day), alcohol use (alcohol units/week), latest clozapine and norclozapine plasma levels, an assessment of physical exercise ("General Practice Physical Activity Questionnaire (GPPAQ)) and scales for symptom severity assessment: Clinical Global Impression for schizophrenia (CGI-S) (Haro et al., 2003) and Global Assessment of Functioning (GAF).

Common clozapine side-effects were also assessed: self-rating of average total number of hours slept daily, which correlates with other objective methods of assessment (Gaina et al., 2004). Assessment included open questions (i.e. on average, how many hours do you sleep daily?), specific questions (i.e. what time do you go to bed/wake up?) and assessment of change (i.e. has your sleep pattern changed since the last appointment?). Over-sedation was considered as equal to or above 9 h of sleep daily.

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