INTRODUCTION

Schizophrenia is a lifelong psychiatric disorder that impairs normal functioning. Patients can present with positive, negative or disorganised symptoms. Despite modern pharmacological advances, 20–30% of patients do not respond to first or second line treatments (Miyamoto et al. 2014). Such treatment resistant patients usually experience profound disability including self-neglect, social isolation and suicide. The efficacy and side effect profile of available antipsychotics for the treatment of schizophrenia vary substantially (Leucht et al. 2013).

The atypical antipsychotic, clozapine, was first developed in 1961 and introduced in Europe in 1970 (De Fazio et al. 2015). It marked a major advancement in psychiatry due to its effective management of negative symptoms in schizophrenia, in addition to reducing suicidality without the increased burden of extra-pyramidal side effects. Clozapine has been shown to be superior in efficacy with 50–60% of patients with previous treatment resistant schizophrenia responding to the medication (Lally et al. 2015). As a result of clozapine’s broad and concerning side effect profile, it is prescribed only when other psychotropic medications have been tried and exhausted. As the relationship between mental and physical health is an intricate one, it is important for physicians to be familiar with the side effects of the medication.

Clozapine was subsequently withdrawn in 1975 after seventeen patients experienced myelosuppression and eight of them died as a result of neutropenic sepsis (De Fazio et al. 2015). Albeit
rare, an overwhelming infection is a well-recognised side effect. It is also important that physicians, particularly psychiatrists and general practitioners who frequently encounter clozapine prescriptions are also aware of the other non-life threatening side effects, which have an impact on patients' quality of life. Clozapine's non-selective pharmacological profile can cause a multitude of side effects as a result of anti-serotonergic, anti-dopaminergic, anti-adrenergic, anti-muscarinic and anti-histaminergic actions (De Fazio et al. 2015).

Clozapine associated nocturnal enuresis (CANE) is a symptom that carries social stigma and may not be easy for a patient to discuss. Only if the physician is aware of the phenomenon can the symptom be sought by direct questioning. Compared to daytime incontinence, the presence of nocturnal enuresis is less likely to be volunteered as a result of the associated embarrassment, and so, patients may suffer in silence or even discontinue the medication. By raising awareness, physicians might better identify and manage the condition and gather more accurate data on prevalence. This would allow early recognition, patient education and management. Compliance would be improved, thus improving mental health and reducing the need for inpatient admission.

To assess the relevance of clozapine associated nocturnal enuresis, the aim of this systematic review was to determine the prevalence of nocturnal enuresis secondary to clozapine use.

METHODS

Literature search

To investigate the prevalence of nocturnal enuresis in patients taking clozapine, a systematic review was conducted using the electronic data source, PubMed. The literature search was performed in March 2018. The search terms used were 'clozapine', 'nocturnal enuresis' and 'urinary incontinence'. Those articles that could not be accessed through OpenAthens were requested through a departmental librarian.

Article selection

Papers that addressed clozapine and nocturnal enuresis were of interest. The inclusion criteria were:

- Relevant articles should report prevalence and could include cross sectional, prospective or cohort studies.
- Patients must be taking clozapine regardless of dose.
- All major psychiatric diagnoses were included.
- Articles that included patients taking other concurrent medications were included.

Exclusion criteria were:

- As this review specifically analysed clozapine's effect on nocturnal enuresis, articles that only examined daytime urinary incontinence and other lower urinary tract symptoms were excluded that examined daytime urinary incontinence and other lower urinary tract symptoms.
- Review articles and case reports were excluded as they did not explore the prevalence of clozapine associated nocturnal enuresis.
- Non-English papers were excluded as a result of our limited language skills.

Data extraction

Data was extracted from the selected papers: author, year of publication, study type, country of study, sample size, age and gender, diagnostic instruments used, clozapine dose, the use of concurrent medications, frequency of nocturnal enuresis, study conclusions and study limitations.

RESULTS

Figure 1 describes the literature search and its outcome.

Eight articles were included in the review.

- Two studies assessed the CANE point prevalence (nocturnal enuresis at the time of assessment) using a cross sectional approach (Centorrino et al. 1994, Long et al. 2015).
- Two studies provided a 1 month prevalence using a retrospective approach (Jeong et al. 2008, Yusufi et al. 2007)
  - A Jeong et al. 2008 assessment was part of a 2-year prospective follow-up study.
  - Harrison-Woolrych et al. 2011 retrospective assessment was part of an observational cohort study.

General and demographical data

The prevalence of clozapine associated nocturnal enuresis ranged from 10–42% (see table 1). Point prevalence was 21–27%, 1-month prevalence was 10–39% and episode prevalence was 15–42%.

The studies included a range of psychiatric diagnoses from schizophrenia, schizoaffective disorder, bipolar affective
disorder, psychotic depression and obsessive compulsive disorder. Only Lin et al. (1999) and Warner et al. (1994) exclusively explored the side effect in patients with schizophrenia alone. Their point prevalence was 41 and 42% respectively.

Study populations were of both inpatient and outpatient groups. There did not appear to be any significant difference between the prevalence of nocturnal enuresis in those patients taking clozapine in the inpatient compared to the outpatient setting (see table 1).

The study sample sizes included in this review ranged from 12 to 103. The study populations were predominantly male, ranging from 60–75% male, aside from the cross sectional by Long et al. (2015), which involved female inpatients from a secure psychiatric facility for women.

Generally, the age ranges of the studies were 16–64 years. Long et al. (2015) included patients up to the age of 70 years old. Mean age ranged from 37 to 41.5 years.

Jeong et al. (2008) observed a higher frequency of nocturnal enuresis in women compared to men. This study was comprised of 60% males. In contrast, Lin et al. (1999) did not find any significant difference between men and women experiencing nocturnal enuresis.

Course and presentation of nocturnal enuresis

Bhirud et al. (2004) observed that participants experienced the symptom either in the first three weeks of initiation or when the dose was increased. Warner et al. (1994) observed that all participants experienced NE within 12 weeks of clozapine initiation regardless of dose.

Two studies described the natural course of CANE as either self-limiting or persistent. Bhirud et al. (2004) observed that 20% of patients self-resolved within an unspecified time and the remainder resolved after an intervention of either dose reduction or with the use of imipramine. Whereas, Warner et al. (1994) observed full resolution of NE in all twelve patients within three months.

Of the patients that admitted to nocturnal enuresis few volunteered the information, highlighting the importance of direct questioning. Yusufi et al. (2007) observed that one in 40 patients who spontaneously reported the symptom of NE on initial general questioning compared to 39 out of 40 positive responses on direct questioning regarding NE. Warner et al. (1994) observed that four out of the five patients that experienced NE did not disclose the symptom during the initial general patient interview, possibly due to embarrassment.

Clozapine dosage and concurrent medications

Six studies elaborated on the mean clozapine dose (see table 1). Yusufi et al. (2007) observed a weak but significant association between clozapine dose and severity of side effects. However, this was not specific to nocturnal enuresis. No other studies elaborated on the relationship between clozapine dose and presence of NE.
Table 1. Description of studies providing episode and point prevalence of clozapine-associated nocturnal enuresis

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Country</th>
<th>Assessment of prevalence</th>
<th>Diagnostic tool</th>
<th>Sample</th>
<th>Diagnoses included</th>
<th>Gender</th>
<th>Mean Age</th>
<th>Clozapine dose</th>
<th>Concurrent Medications</th>
<th>Prevalence of CANE</th>
<th>Conclusion</th>
<th>Limitations</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centorrino, Baldessarini, Kando et al 1994</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>Patient interview conducted by a psycho-pharmacologist</td>
<td>44 outpatients receiving weekly clozapine monitoring</td>
<td>Schizophrenia, schizoaffective disorder, BPD, psychotic depression</td>
<td>75% male</td>
<td>37</td>
<td>Mean 294mg/day Range: 12.5-900mg</td>
<td>Benzodiazepines, lithium, antidepressants</td>
<td>27% point prevalence</td>
<td>High frequency of CANE in those taking clozapine</td>
<td>Did not investigate other causes of CANE</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Long, West, Siddique et al 2015</td>
<td>United Kingdom</td>
<td>Cross-sectional</td>
<td>Patient interview. Unvalidated six-item questionnaire. Information received from case notes or the care coordinator</td>
<td>72 women in a secure psychiatric setting taking clozapine</td>
<td>Schizophrenia, schizoaffective, depression, personality disorders, PTSD</td>
<td>100% female</td>
<td>35.6</td>
<td>Not specified</td>
<td>Not specified</td>
<td>21% point prevalence</td>
<td>CANE and urinary incontinence (UI) are prevalent amongst those taking psychotropic medication</td>
<td>Other causes of CANE not investigated. Did not investigate if NE was present prior to initiation of antipsychotic medication</td>
<td>Recall bias. Selection bias. Limited generalisability</td>
</tr>
<tr>
<td>Jeong, Kim, Ahn et al 2008</td>
<td>Korea</td>
<td>Retrospective assessment of 1 month prevalence of CANE</td>
<td>Patient interview. 7-item International prostate symptom score questionnaire. Barry et al. (1992)</td>
<td>101 outpatients taking a stable dose of clozapine</td>
<td>Schizophrenia, bipolar disorders, major depression, OCD</td>
<td>60% male</td>
<td>31.1</td>
<td>Mean dose 304.2mg</td>
<td>Not specified</td>
<td>10% 1 month point prevalence</td>
<td>Lower urinary tract symptoms are prevalent in those taking clozapine. LUTS worsened by 11% over subsequent 2 years.</td>
<td>Did not investigate if NE was present prior to initiation of antipsychotic. Did not specify if CANE changed over the 2 year period.</td>
<td>Recall bias. Participants aware of the study aims.</td>
</tr>
</tbody>
</table>
### Table 1. Description of studies providing episode and point prevalence of clozapine associated nocturnal enuresis

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<tr>
<td>Yusufi, Mukherjee, Flanagan et al 2007</td>
<td>United Kingdom</td>
<td>Retrospective assessment of 1 month prevalence of CANE</td>
<td>Patient interview, 35 item questionnaire using the Antipsychotic non-neurological side effects rating scale. Ohlsen et al. (2008)</td>
<td>103 outpatients receiving clozapine monitoring in one trust</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>69% male</td>
<td>Mean 39.3 Range 18-65</td>
<td>Mean 456mg/day</td>
<td>Mood stabiliser, anticholinergics, antidepressant, second antipsychotic, anxiolytic or hypnotic.</td>
<td>39% 1 month point prevalence</td>
<td>Clozapine plasma levels were weakly correlated with presence and severity of side effects. Direct questioning required to illicit side effects.</td>
<td>Did not investigate other causes of CANE.</td>
<td>Study design bias</td>
</tr>
<tr>
<td>Bhirud, Shah 2004</td>
<td>India</td>
<td>Retrospective</td>
<td>Patient interview. Asked for the presence of NE since starting clozapine</td>
<td>100 consecutive patients on clozapine in a hospital setting</td>
<td>Schizophrenia and bipolar affective disorder</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Mood stabiliser, anticholinergics, antidepressant, second antipsychotic, anxiolytic or hypnotic.</td>
<td>15% episode prevalence since starting clozapine</td>
<td>CANE started within 3 weeks of clozapine initiation or when dose was increased</td>
<td>Did not investigate other causes of CANE.</td>
<td>Recall bias, Reporting bias</td>
</tr>
<tr>
<td>Harrison-Woolrych, Squeg, Ashton et al 2011</td>
<td>New Zealand</td>
<td>Retrospective</td>
<td>Patient interview conducted by medical or nursing staff. Questionnaire based on the Intensive medicines monitoring programme. Harrison-Woolrych et al. (2007)</td>
<td>91 patients from one urban district taking clozapine.</td>
<td>Schizophrenia, affective disorders, Neurotic disorders and other</td>
<td>60% male</td>
<td>Mean 39.1 Range 18-64</td>
<td>Not specified</td>
<td>Mood stabiliser, anticholinergics, antidepressant, second antipsychotic, anxiolytic or hypnotic.</td>
<td>62% of patients taking clozapine took other medications that act on the central nervous system</td>
<td>20.7% of new cases of NE since starting treatment</td>
<td>Episode prevalence of CANE is one fifth after varying lengths of treatment</td>
<td>Small sample size, Did not investigate other causes of CANE.</td>
</tr>
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Table 1. Description of studies providing episode and point prevalence of clozapine associated nocturnal enuresis

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<tr>
<td>Lin, Bai, Chen et al 1999</td>
<td>China</td>
<td>Retrospective</td>
<td>Patient interview with psychiatrist.</td>
<td>61 inpatients from one hospital</td>
<td>Schizophrenia</td>
<td>61% male</td>
<td>37</td>
<td>Mean dose 390.2mg</td>
<td>Benzodiazepenes, antidepressants, lithium, anticholinergics, antipsychotics, anticonvulsants</td>
<td>41% episode prevalence since starting clozapine</td>
<td>CANE may be persistent</td>
<td>Did not explore other causes of CANE</td>
<td>Recall bias, Small sample size</td>
</tr>
<tr>
<td>Warner, Harvey, Barnes 1994</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>Patient interview.</td>
<td>12 inpatients and outpatients receiving clozapine under one clinical team</td>
<td>Schizophrenia</td>
<td>67% male</td>
<td>41.5</td>
<td>Mean dose 396mg Range 300-750mg</td>
<td>Not specified</td>
<td>42% episode prevalence since starting clozapine</td>
<td>CANE started within three months of clozapine initiation. CANE is underreported</td>
<td>Did not explore other possible causes of CANE</td>
<td>Recall bias, Small sample size</td>
</tr>
</tbody>
</table>
Bias

Potential of Recall bias in studies included

All studies that utilised a questionnaire based patient interview approach were exposed to recall bias, as it heavily relied on accurate patient recollection and timing of symptom events. Particularly the studies that reported an episode prevalence since clozapine initiation. This applied to both patients and healthcare staff when asked to clarify the presence or absence of NE.

Generally, the studies did not explicitly document the time period over which the presence of NE was assessed during the patient interview, that is, whether the symptom was experienced currently, within the last week, since clozapine initiation or at any point over their lifetime. Jeong et al. (2008) and Yusufi et al. (2007) clearly documented that the questions were asked in relation to the past month.

Ascertainment bias

Ascertainment bias was present in the four studies that had used unvalidated questionnaires as their diagnostic tool. All the studies included a face-to-face patient interview, although the person who conducted the interview was not always specified. Centorrino et al. (1994), Lin et al. (1999) and Harrison-Woolrych et al. (2011) utilised the experience of trained psychopharmacologists, psychiatrists and mental health nurses to perform the interviews (see table 1).

Lack of standardisation and generalisability

There were differences in how the prevalence was evaluated. Four studies determined the prevalence by relying on accurate patient recall since starting clozapine. The remaining four studies used a point or 1-month point prevalence.

DISCUSSION

This is the first systematic review to investigate the prevalence of clozapine associated nocturnal enuresis. The prevalence ranged from 10–42% and compared to other antipsychotics clozapine was more likely to cause NE. Point prevalence was 21–27%, 1-month prevalence was 10–39% and episode prevalence was 15–42%.

Sagy et al. (2014) has cited a prevalence of CANE to be as low as 0.23% by Sandoz, a finding which remains unpublished and so cannot be validated. The large range of the prevalence is likely to be attributable to the differing study design, inclusion criteria and...
diagnostic tools used to determine the presence of NE. The highest rates were found in the studies that included smaller sample sizes and inpatient populations, suggesting that the severity of mental illness may have an effect on the presence of NE.

Inpatient and outpatient populations

No previous studies have compared the rate of CANE between the inpatient and outpatient populations. Although it is difficult to compare the studies as a result of differing study designs, there does not appear to be a significant difference between the patient populations (see table 1).

Other side effects of clozapine

Compared to the other side effects, nocturnal enuresis seems to be relatively prevalent. Among clozapine's other side effects, sedation and hypersalivation are the most commonly experienced affecting 70% and 57% of patients, respectively (Yusufi et al. 2007). Sexual dysfunction and nocturnal enuresis, although not often disclosed, occur with a higher frequency (55% and 39%) ahead of other more well recognised side effects, such as constipation and weight gain (34% and 31%) (Yusufi et al. 2007). In future studies, it would be of benefit to examine the rate of daytime urinary incontinence associated with clozapine use.

Nocturnal enuresis in the general population

The prevalence of NE in the population taking clozapine medication is considerably higher than the general population. A telephone survey of 8,500 adults aged 16–40 years by Yeung et al. (2008) found the prevalence of nocturnal enuresis in the general population to be over 2%. This review estimates that the prevalence of clozapine associated nocturnal enuresis to be 10–42%. As the patient population who require clozapine have risk factors for urinary incontinence, including psychosis itself, it is difficult to ascertain an accurate prevalence of true CANE. Hsu et al. (2007) conducted a study involving 30,000 participants and discovered that the patients with schizophrenia had a 1.78 fold risk increase of urinary incontinence compared to the patients without schizophrenia after accounting for co-morbidities and medication.

Criteria needed to establish CANE prevalence in future studies

From the assessed publications, it was difficult to ascertain if clozapine was the primary cause for nocturnal enuresis, as no single study clearly meets the above mentioned criteria to arrive at an accurate prevalence. Although only three studies’ aims (Harrison-Woolrych et al. 2011, Bhirud et al. 2004 and Warner et al. 1994) were to determine the prevalence of clozapine associated nocturnal enuresis, a more rigorous patient selection and prospective design would help ascertain a true prevalence.

In order to give a true prevalence of CANE, we suggest future studies to incorporate the following criteria:

- Nocturnal enuresis must have developed after clozapine initiation.
- Other causes for NE should be explored such as the use of diuretics, presence of a urinary tract infection, urge and stress incontinence, benign prostatic hypertrophy, epilepsy, cognitive impairment, neurological disability, diabetes mellitus, diabetes insipidus and psychosis itself. Only Long et al. (2015) attempted to explore the alternative causes of new incontinence. Clozapine associated nocturnal enuresis should only be considered once the mentioned have been excluded.
- The diagnostic tool was used to determine the presence of nocturnal enuresis. Those studies that relied solely on patient recall had less power than those that used a validated questionnaire during the interview setting.
- The temporal relationship between clozapine initiation and the timing of NE development is important as a symptom that develops soon after an intervention is more likely to be due to the intervention.
- To produce a true prevalence, all patients should ideally be prescribed clozapine alone. However, as co-morbidity and polypharmacy are common in patients taking clozapine medication, it can be difficult to ascertain the cause and effect. To reduce confounding, the four studies highlighted relevant co-existing medications. The articles reviewed on NE caused by concurrent use of both psychiatric and non-psychiatric medications were few, thus reducing the impact of a true prevalence.

To elicit the prevalence of CANE in future studies, a prospective approach should be adopted. Patients should be identified prior to clozapine initiation and subsequently interviewed at regular intervals post-initiation. As clozapine initiation often requires inpatient management, it would be possible to enquire about specific symptoms frequently during medicine rounds before clozapine is dispensed, similar to how routine physical observations are recorded. Although, it may add to workload and additional checklists, it is important to recognise such side effects early in order to improve compliance and overall mental health.
Mechanism of CANE

The cause of nocturnal enuresis secondary to clozapine use is considered to be multifactorial. A collection of three case studies by Kho et al. (2011) describes how nocturnal enuresis developed through differing mechanisms. Clozapine's sedative effect was observed in a female patient with schizophrenia who was found to sleep too deeply to empty her bladder. The seizure threshold is also lowered by the antipsychotic and nocturnal seizures may cause incontinence. All antipsychotics, in particular clozapine, increase insulin resistance and polyuria secondary to diabetes may cause incontinence. To further confound the clinical presentation, incontinence may be a symptom of psychosis itself (Warner et al. 1994.).

The precise mechanism of how clozapine affects the bladder is under speculation. Clozapine's anti-cholinergic effect on the detrusor muscle and anti-adrenergic effect on the urethral sphincter are demonstrated by the following case reports.

Cohen et al. (1994) describes the case of a 38 year old man with paranoid schizophrenia who developed nocturnal enuresis secondary to urinary retention. He was subsequently catheterised, and four litres of urine was drained. It was believed that clozapine's strong anti-cholinergic effect was attributable to the urinary retention.

Fuller et al. (1996) managed clozapine induced daytime urinary incontinence with an alpha agonist, ephedrine, in order to counteract clozapine's anti-adrenergic effect on the internal bladder sphincter. Of the 16 cases that were treated with ephedrine, twelve had complete resolution of symptoms and three had partial improvement. The participants were aware of the study aims and the presence of incontinence was determined either by urine stained linen or patient complaint.

REFERENCES


De Fazio P, Gaetano R, Caroleo M, Cerminara G, Maida F, Bruno A, Muscatello MR, Moreno MJ, Russo E, Segura-García C. Rare and

Clozapine to treat urinary incontinence

It is worth noting that three papers were excluded in the screening process as clozapine was observed to treat urinary incontinence. Balhara et al. (2011) describe a case study where the use of clozapine was used to successfully manage a schizophrenia patient's urinary incontinence. However, on clozapine titration, the urinary incontinence reappeared when the dose exceeded 300 mg per day. Kumar et al. (2007) and Mathew et al. (1996) describe similar cases. It is likely that incontinence was attributable to psychosis, which subsequently improved with clozapine. And the reason for the reoccurrence at higher doses of clozapine may be due to clozapine induced urinary incontinence.

CONCLUSION

Nocturnal enuresis is an under-reported and under recognised side effect of clozapine. It impacts negatively on quality of life and contributes to reduced compliance in a patient population that already experiences management difficulties. The life-threatening side effects of clozapine are well-recognised; however, greater awareness of lesser known side effects are still needed. Future studies with a prospective design, greater sample size and carefully selected control groups are still needed to establish a true prevalence of clozapine associated nocturnal enuresis.

Declaration of interest: None of the authors have any interest to declare in relation to this paper.

Ethical approval and informed consent not required for systematic literature review.
Nocturnal Enuresis is an Under-recognised Side Effect of Clozapine:
Results of a Systematic Review


