Clozapine use in old-age psychiatry – a retrospective audit and prospective survey

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Introduction

- Clozapine is a useful alternative treatment option for elderly individuals with refractory primary psychosis.

- However, despite an ageing population and a high prevalence of psychotic disorders in the elderly, there is a dearth of published data regarding the use of clozapine in old age.
Introduction

- Different dose range for schizophrenia and psychotic disorders vs Parkinson’s disease associated psychosis.

- Comorbid illnesses, drug interactions and increased risk of adverse drug reactions.

- Aging is known to affect pharmacokinetic and pharmacodynamic parameters.
Aims and objectives

- Audit comparing the rate of titration of clozapine in patients aged 65 years and above with a standard clozapine titration protocol used by the Waitemata district health board (WDHB)

- When clozapine titration differed from the standard protocol a retrospective review of the patient notes was carried out to determine potential causes.

- An electronic survey was conducted to assess clinician attitudes
Method

- A retrospective chart review was conducted of all patients who had been initiated on clozapine at the age of 65 years or above, from the 1st of January 2007 to the 31st of July 2017.

- Exclusion criteria were: i) discharge from WDHB during the period of titration of clozapine; ii) stopping clozapine for reasons other than side effects or intolerance during the titration period, and iii) death during the titration period of clozapine not linked to the medication.
Method

- Clozapine titration rate in the elderly was compared with a standard titration protocol published in The Clozapine Handbook by Bleakley and Tylor in 2013 26(pp26,27,28,29) which is incorporated in the WDHB best practice guidelines for clozapine use.

- According to this schedule the target dose of clozapine for elderly patients with treatment resistant schizophrenia is 250mg/day attained by day 13 of titration for inpatients, and day 22 of titration for outpatients.
Method

- The initial dose of clozapine, peak dose at the end of titration and days elapsed from initial to peak dose during titration were compared between the study group and the standard protocol using one-sample t-tests.

- The survey covered five domains: i) demographics of the participants, ii) indications for clozapine use in elderly iii) rate of titration of clozapine in older people, iv) potential factors that could limit the use of clozapine in the elderly and v) factors that could enhance clozapine use in older people.
Results

- A total of 40 elderly patients had been initiated on clozapine during the study period.
- None of the patients met the exclusion criteria.
- Clozapine titration in all 40 patients did not adhere to the standard protocol and was guided by tolerance to side effects and clinical response.
- Hence the end point for titration was considered when a stable dose was reached and discharge planning was commenced for inpatients; and when a stable dose was reached with clinical improvement recorded by the treating clinician for outpatients.
The mean age at initiation of clozapine was 74.78 years (SD +/- 7.09).

Of the study sample, 42.5% were men (n=17) and 57.5% were women (n=23)
Indications for clozapine

- Dementia with BPSD: 1 patient
- Treatment resistant bipolar disorder: 2 patients
- Severe tardive dyskinesia: 3 patients
- Psychosis associated with Parkinson's disease and Lewy body dementia: 19 patients
- Treatment resistant psychosis: 15 patients

Number of patients
Location of clozapine titration

- Inpatient: n=33
- Rest home: n=7
Results

- The mean dose at initiation in the elderly was 10.94 mg (SD +/- 4.41).
- The initial daily dose according to the standard protocol was 12.5mg.
- The mean starting dose for patients with a diagnosis of psychosis associated with Parkinson’s disease or Lewy body dementia was 9.34 mg (SD +/- 3.26).
- The mean dose at initiation for all other patients was 11.75 mg (SD +/- 4.88).
- The peak (maximum) dose for all patients was 69.31 mg (SD +/- 68.45).
- The peak dose for patients with Parkinson’s disease or Lewy body dementia was 32.43 mg (SD +/- 16.84).
- The peak dose for all other patients (n=21) was 104.17 (SD +/- 78.79).
Peak dose range for patients on clozapine
Results

- Clozapine titration for inpatients and outpatients was compared with the standard titration protocol.

- The peak dose of clozapine at the end of the titration period for all inpatients was 74.24 mg.

- The mean number of titration days to attain this dose was 26.54 (SD +/- 17.98). This was compared with the standard protocol, dose = 250 mg and number of days = 13.
Results

- Time taken to reach the peak dose in older inpatients patients was significantly slower than the standard protocol (one sample t = 4.33, p < 0.0001).

- The peak dose of clozapine for all outpatients at the end of titration was 50.53 mg. The mean number of titration days were 34.27 (SD +/- 13.14).

- According to the standard protocol the dose to be attained was 250 mg over 22 days. The difference in the number of titration days was statistically significant (one sample t = 2.47, p < 0.05).
Results

- In the current study, the dose of clozapine at the end of titration for patients with Parkinson’s disease and Lewy body dementia was 32mg/day.
- The stable dose for other patients with psychosis or mood disorders was 104mg/day which was in keeping with previous studies.
- A proxy marker of efficacy was that 35 out of 37 patients (94.6%) who continued clozapine titration recovered to the point where discharge planning was commenced for inpatients or a clear clinical improvement was recorded for outpatients.
Range of medical comorbidities. Figure-6

- Epilepsy: 3
- Osteoarthritis of spine or lower limbs: 16
- Chronic constipation: 18
- Dyslipidemia: 12
- Cerebrovascular accident: 13
- Hypertension: 15
- Parkinson's disease: 19
- Diabetes mellitus: 7
- Ischemic heart disease: 9

Number of patients
Range of side-effects to clozapine

- Nocturnal urinary incontinence: 2
- Tiredness: 2
- Dry mouth: 1
- Postural hypotension: 1
- Pericarditis: 1
- Myocarditis: 1
- Sweating: 1
- Pneumonia: 2
- Extrapyramidal side-effects: 2
- Sedation: 15
- Unsteadiness: 8
- Dizziness: 7
- Fall: 7
- Salivation: 7
- Constipation: 24

Number of patients
Results

- A total of five patients (12.5%) discontinued clozapine during the titration period.

- The reasons for discontinuation were side effects (n=3) and poor response (n=2).

- The side effects requiring discontinuation were i) myocarditis (n=1), ii) pericarditis (n=1), iii) excessive sedation and postural hypotension (n=1). There were no deaths recorded during clozapine titration.
Results: Survey

Age group of survey respondents

- 36-45 years: 44.4%
- 46-55 years: 33.3%
- 56-65 years: 14.9%
- 66-75 years: 7.4%
Results: Survey

Years worked as consultant psychiatrist

- 33.3% 0-5 years
- 22.2% 6-10 years
- 11.2% 11-15 years
- 25.9% 16-20 years
- 7.4% 21 and above
Indications for clozapine use

- Dementia with BPSD
- Psychosis along with severe tardive dyskinesia
- Psychosis in Parkinson's disease
- Treatment resistant bipolar disorder
- Treatment resistant schizo-affective disorder
- Treatment resistant schizophrenia

Legend:
- Not indicated
- Unsure
- Indicated
Factors limiting clozapine use in the elderly

- Concerns about medication interactions
- Concerns about existing medical co-morbidity
- Limited personal experience
- Limited published data
- Inpatient hospital admission for titration
- Long period of titration
- Concerns regarding tolerability
- Concerns regarding efficacy

For each factor, the blue bars indicate the percentage of respondents who probably limit its use, and the green bars indicate the percentage who definitely limit its use.
Factors facilitating clozapine use in the elderly

- Dedicated staff to monitor clozapine
- Dedicated day hospital placement beds
- Dedicated hospital beds for clozapine initiation
- Optimised clozapine titration protocol
- Dedicated guidelines for elderly
- Information regarding clozapine use in elderly

[Bar chart showing percentages for each factor]
Conclusion

- Clozapine titration in the study group was significantly slower than current protocols

- A low initial dose and slower titration rate to allow the patient to adjust to side effects could improve tolerability

- A proxy marker of efficacy was that 35 out of 37 patients (94.6%) who continued clozapine titration recovered

- An attempt should be made to limit polypharmacy as well as assess for potential medication interactions prior to commencing clozapine to improve outcomes
Conclusion

- A baseline record of comorbid medical conditions should be maintained to determine if side effects can be clearly attributed to clozapine use.

- A structured approach to clozapine use in the elderly and additional research can improve psychiatrists’ knowledge about the role and limitations of clozapine use in the elderly.