

# Prescribing Clozapine for Psychosis in Parkinson's Disease

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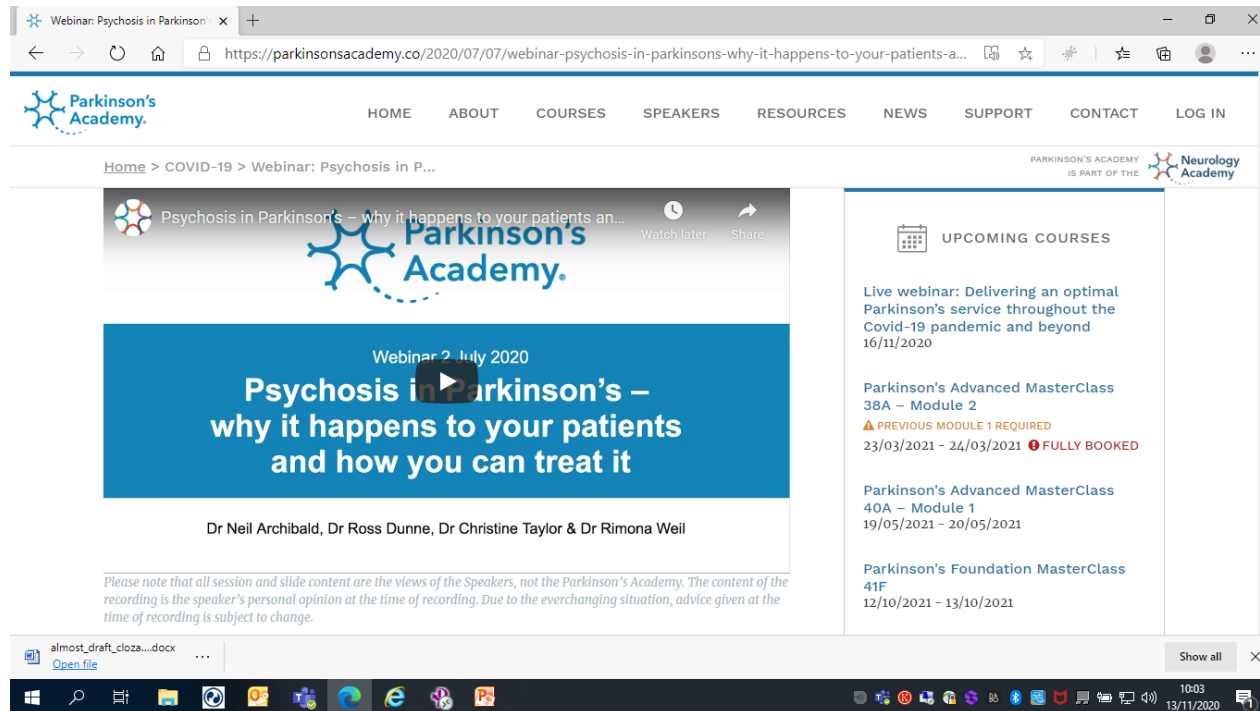


# Contents

- I will cover briefly:
  - A structured approach to the assessment of psychosis in Parkinson's disease
  - The evidence base for management of Parkinson's psychosis
  - The role of clozapine in this setting and how services can be structured to use this safely

# Psychosis in Parkinson's – why it happens to your patients and how you can treat it – Parkinson's Academy Webinar

- <https://www.youtube.com/watch?v=Dp-wtaR43I4>



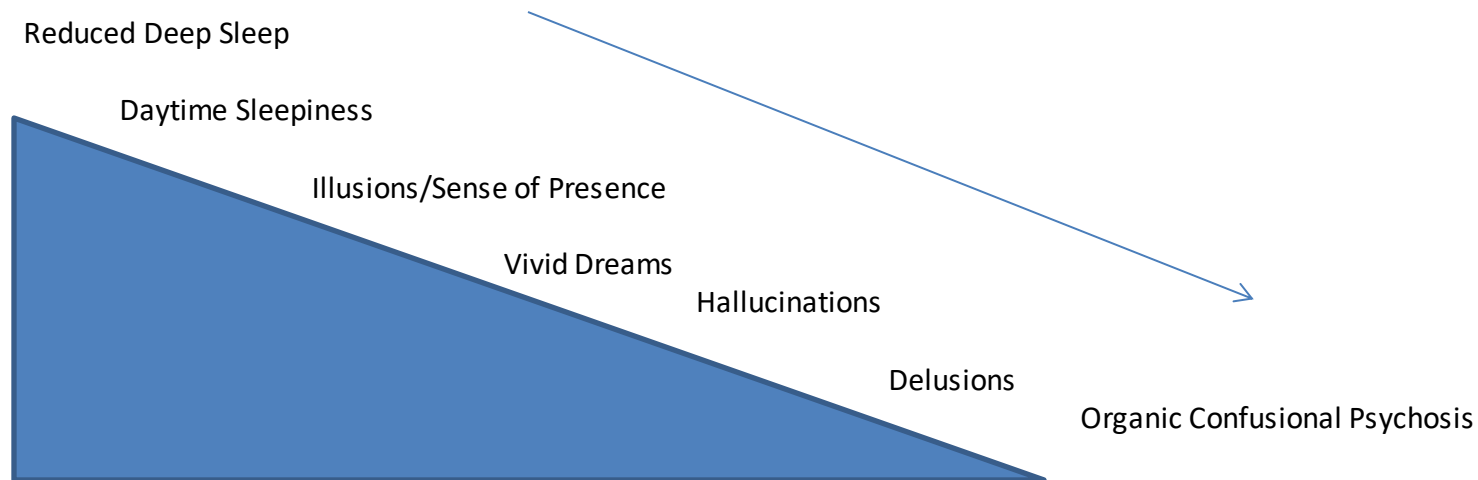
The screenshot shows a web browser displaying the Parkinson's Academy website. The page is titled "Webinar: Psychosis in Parkinson's" and features a large blue banner with the text "Webinar 2 July 2020 Psychosis in Parkinson's – why it happens to your patients and how you can treat it". Below the banner, the speakers are listed as "Dr Neil Archibald, Dr Ross Dunne, Dr Christine Taylor & Dr Rimona Weil". A disclaimer at the bottom of the banner reads: "Please note that all session and slide content are the views of the Speakers, not the Parkinson's Academy. The content of the recording is the speaker's personal opinion at the time of recording. Due to the everchanging situation, advice given at the time of recording is subject to change." On the right side of the page, there is a section titled "UPCOMING COURSES" with three entries: "Live webinar: Delivering an optimal Parkinson's service throughout the Covid-19 pandemic and beyond 16/11/2020", "Parkinson's Advanced MasterClass 38A – Module 2 23/03/2021 – 24/03/2021 FULLY BOOKED", and "Parkinson's Advanced MasterClass 40A – Module 1 19/05/2021 – 20/05/2021". The bottom of the page shows a Windows taskbar with various application icons and the system clock displaying 10:03 on 13/11/2020.

# Setting up a clozapine service for Parkinson's psychosis

- Upcoming article
- Authors: Christine Taylor, Alison Marsh-Davies, Rob Skelly, Neil Archibald, Sarah Jackson
- Watch this space!!!!

# Assessment

- Psychotic symptoms in Parkinson's disease are common and not all will require intervention
- One useful concept is to consider them occurring on a clinical spectrum – the so-called neuropsychiatric “slippery slope” (Playfer 2008)



- The further along the spectrum they are, the more likely it is insight will be affected and patient will be distressed
- Hallucinations in Parkinson's disease are usually visual in nature but can occur in all other modalities

# Management

- Do not treat if the symptoms are well tolerated by the patient
- In clinical practice patients with complex psychosis can sometimes quickly exhaust treatment options
- They may show a partial response to treatment with Quetiapine but remain symptomatic and distressed by their symptoms.
- There is a good evidence base supporting the use of Clozapine but the practicalities of prescribing can remain a barrier

# Management

- **The Principles of management of Parkinson's disease psychosis: "ERA"**
- **(Playfer 2008)**
- **Exclude delirium** – Screen for inter-current physical illness
- **Explain to the carer** – Worries the carer more than the patient!
- **Reduce sensory and deprivation sensory overload** –adequate lighting, avoid excessive patterned furniture and fittings. Optician review.
- **Reduce drugs** - cautiously and in a step wise manner. (Consider reducing the last drug added first. It can be useful to reduce Parkinson's drugs in the following order: Anticholinergics, Tricyclics, MAOB, Amantadine, other antidepressants, Dopamine agonists, COMT, Apomorphine and L-Dopa)
- **Antipsychotics** – careful use of quetiapine or clozapine. Monitor ECG, cognitive and motor function. Do not use traditional antipsychotics.
- **Acetylcholinesterase inhibitors** – careful use monitoring cognition and motor function

# NICE guidance 71

- **Nice Guidance 71 (2017) recommends the following management of psychotic symptoms (hallucinations and delusions):**
  - **Reduce PD meds where possible**
  - **Consider quetiapine**
  - **If standard treatment is not effective, offer clozapine**
  - **Be aware that lower doses of quetiapine and clozapine are needed for people with Parkinson's disease than in other indications.**



# NICE guidance 71

- **Nice Guidance 71 (2017) recommends the following management of psychotic symptoms (hallucinations and delusions) (cont):**
  - **Do not offer olanzapine**
  - **Recognise that other antipsychotic medicines can worsen the motor features of Parkinson's disease**
  - **For guidance on hallucinations and delusions in people with dementia, see managing non-cognitive symptoms in the NICE guideline on dementia:**
    - **consider rivastigmine – has shown effectiveness in improving behavioural symptoms in PDD but not in patients whose symptoms are predominantly psychotic**

# Clozapine Evidence Base

- **The Parkinson Study Group (1999)**
- Randomized, double blind, placebo-controlled trial of low doses of clozapine in patients with drug induced psychosis in Parkinson's disease.
- 60 patients included – 30 treatment and 30 placebo
- Range of 6.25mg to 50mg clozapine per day with a mean daily dose of 24.7mg.
- Three patients withdrew from each group
  - In the placebo arm, 2 withdrew from the study due to the worsening of their psychiatric condition and the other due to being hospitalized for pneumonia.
  - In the clozapine treatment group 3 patients withdrew from the study, one discontinued the drug due to leukopenia, one because of myocardial infarction and the other because of sedation.

# Clozapine Evidence Base

- The Parkinson Study Group (1999) (cont)
- Clozapine treatment group showed significant improvement in their psychotic symptoms using a number of measures
- Clozapine treatment improved tremor and had no deleterious effect on the severity of parkinsonism
- Clozapine at daily doses of 50mg or less in this patient group is safe and significantly improves drug-induced psychosis in Parkinson's disease without worsening parkinsonism

# Clozapine Evidence Base

- The use of Clozapine in Parkinson's disease related psychosis is supported by NICE Quality Standard 164 (NICE 2018):
  - “Services for adults with Parkinson's disease provide access to clozapine and patient monitoring for treating hallucinations and delusions.”
  - They recognise that medicines for Parkinson's disease can cause hallucinations and delusions and if not controlled adequately they can lead to admission to care homes.
  - This quality standard recognises that specialist Parkinson's disease services may not be able to provide a Clozapine service directly and should agree with other local services how access will be provided and ensure that specific needs of adults with Parkinson's disease (such as the need for a lower dose) are understood and met.
- Unfortunately however there is very limited provision nationally of Clozapine services suitable for patients with Parkinson's disease and this NICE Quality Standard offers no care pathway or guidance on how to implement it.

# Clozapine Evidence Base

- “Update on treatments for nonmotor symptoms of Parkinson’s disease – An evidence-based medicine review” Seppi et al (2019)
  - Clozapine is efficacious in the treatment of psychosis in Parkinson’s disease and that it carries acceptable risk with specialised monitoring and that it is clinically useful
  - Quetiapine is reported to have insufficient evidence but that it carries acceptable risk without specialised monitoring and is possibly useful
  - No other antipsychotics are deemed efficacious or safe in Parkinson’s disease because of the associated risk of extra-pyramidal side effects.

# SPC for Clozapine in PD Psychosis

- Starting dose must not exceed 12.5mg/day in the evening
- Dose increments of 12.5mg, maximum of twice a week up to maximum dose of 50mg, a dose that should not be reached until the end of the second week
- Give as a single dose in the evening
- Only use >50mg/day in exceptional cases and never >100mg/day
- Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs
- Blood pressure should be monitored during the first weeks of treatment (the licence does not specify how often this should be done)
- Ending therapy - A gradual reduction in dose by steps of 12.5mg over a period of at least one week or preferably two is recommended. Treatment must be ended immediately in the event of neutropenia or agranulocytosis with careful psychiatric monitoring due to risk of recurrence of symptoms

# Who could offer clozapine to patients with Parkinson's psychosis?

Movement Disorder Services	Adult Mental Health Services	Old Age Psychiatry Services
<ul style="list-style-type: none"> <li>· Expertise in managing Parkinson's disease and Parkinson's medications</li> <li>· Comfortable with managing co-morbidities</li> <li>· Used to making alterations in Parkinson's drugs</li> <li>· Knowledge of the patient with Parkinson's disease as tend to follow up patients for the lifetime of their disease</li> <li>· Offer ongoing support for the person with Parkinson's disease</li> <li>· Little knowledge or experience of prescribing Clozapine</li> </ul>	<ul style="list-style-type: none"> <li>· Expertise in managing psychosis and prescribing Clozapine but in higher doses in the context of treatment resistant schizophrenia</li> <li>· Have the infrastructure for the monitoring requirements and dispensing of Clozapine</li> <li>· May only have access to initiate Clozapine in hospital settings depending on configuration of services</li> <li>· Less expertise at managing Parkinson's disease and other comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>· Expertise in diagnosis and management of dementia</li> <li>· May be more comfortable with the management of Parkinson's disease</li> <li>· Offer routine community follow up with Community Mental Health Teams including Community Psychiatric Nurses</li> <li>· Have expertise in managing psychosis but may not have as much experience in prescribing Clozapine in their older population</li> <li>· Have the infrastructure for the monitoring requirements and dispensing of Clozapine</li> <li>· May only have access to initiate Clozapine in hospital settings depending on configuration of services</li> </ul>

# Barriers to Clozapine Use

- Requires a named prescriber
- Need for regular blood testing
- Need for physical observation monitoring on commencing
- Postural hypotension, hypersalivation and constipation are common side effects, also common in PD
- Lack of experience of community initiation or of clozapine in general
- Dispersed expertise
- Heterogeneity of services
- No blue print for the development of services
- Protocols for the use of clozapine in Treatment Resistant Schizophrenia are not suitable for Parkinson's psychosis
- Disjoined care between physical and mental health Trusts



# **Clozapine Initiation and titration in Mental Health Services for Older People (MHSOP)**

## **Teesside – Dr Neil Archibald**

- Involvement of MH Trust
- Initiate 6.25mg nocte for at least 7-14 days
- CPN review day 1 for pulse/BP check
- Review OPC day 7 for pulse/BP/FBC check
- Titration as required
- Usual dose 12.5mg-100mg nocte

# Clozapine Initiation and titration in Mental Health Services for Older People (MHSOP)

## Teesside – Dr Neil Archibald

- 5 years experience and approx. 25 patients treated
- Rarely need to exceed 50mg and treatment response typically seen within 4-6 weeks
- Improvements with psychosis and additional benefits with improving sleep and anxiety
- To date no cases of agranulocytosis and only a very small number of “amber” blood results
- Confidence has grown with community initiation
- A number of patients stopped clozapine due to problems with balance or drowsiness
- Several other patients stopped the medication due to lack of efficacy

# Royal Devon and Exeter Clozapine Service – Dr Sarah Jackson

- Currently have 10 patients who are actively being treated with clozapine
- Have treated 45 patients since 2010.
- No issues to date with red or amber results
- Patients often develop hypersalivation, constipation and a postural drop but not necessitating the discontinuation of clozapine
- The average dose used in this patient cohort is 12.5mg-25mg once a day.

# **Clozapine Initiation at Parkinson's Service Specialist Rehabilitation Derby – Dr Rob Skelly and Dr Christine Taylor**

- Similar model
- Delayed due to COVID
- Clozapine will be dispensed by the mental health Trust pharmacy and prescribed and monitored in the PD service
- Clozapine is started on a Sunday evening so patient can attend for physical observation monitoring on Monday and Tuesday
- Patients will attend for weekly blood testing on a Tuesday and attend on Friday for review and collection of a weekly prescription
- Dose titration will be carried out very slowly with patients starting on 6.25mg and doses will only be increased every 2 weeks as a minimum

# Conclusion

- Complex area of clinical practice
- Carries with it a large burden on quality of life and is predictor of need for 24 hour care
- Treatment options are limited and clozapine is the most effective treatment however in practice can be difficult to prescribe due to the monitoring requirements and dispersed expertise and lack of services
- It is possible to set up safe outpatient clozapine initiation services which greatly benefit a small number of patients
- You are very welcome to contact me to discuss further on [christine.taylor31@nhs.net](mailto:christine.taylor31@nhs.net)

# References

- Chaudhuri K, Healy D and Schapira H (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet neurol* 2006;5:235-45.
- Kuzuhara S (2001). Drug-induced psychotic symptoms in Parkinson's disease. Problems, management and dilemma. *Journal of Neurology*. 248 (suppl3):III28-31.
- National Institute for Health and Care Excellence (2017). Parkinson's disease in adults (Nice Guideline 71). Available at <https://www.nice.org.uk/guidance/ng71> (accessed 18th September 2020).
- National Institute for Health and Care Excellence (2018). Parkinson's disease (NICE Quality Standard 164). Available at <https://www.nice.org.uk/guidance/QS164> (accessed 18th September 2020).
- Parkinson Study G. (1999). Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med*. 1999; 340: 757- 763.
- Playfer J, Hindle J. (2008). Parkinson's disease in the older patient. Radcliffe Publishing.
- Seppi K, Chaudhuri R, Coelho M, Fox S, Katzenschlager R, Lloret S, Weintraub D, Sampaio C. (2019). Update on treatments for nonmotor symptoms of Parkinson's disease – An evidence based medicine review. *Movement disorders*, vol 34, No 2, 2019.
- Summary of Product Characteristics (SmPC) for Clozaril. Last updated April 2020. Accessed at <https://www.medicines.org.uk/emc/product/4411/smpc/> (accessed 6<sup>th</sup> October 2020).
- Summary of Product Characteristics (SmPC) for Denzapine. Last updated November 2019. Accessed at <https://www.medicines.org.uk/emc/product/6120/smpc> (accessed 6<sup>th</sup> October 2020)
- Summary of Product Characteristics (SmPC) for Zaponex. Last updated June 2020. Accessed at <https://www.medicines.org.uk/emc/product/7715/smpc> (accessed 6<sup>th</sup> October 2020)
- Taylor C. (2020). Mental Health Matters Too – Integration of Physical and Mental Health in a Multidisciplinary Parkinson's Clinic. SIG 2018 Derby. Parkinson's UK.