

2020 年 4 月 10 日

厚生労働省 医薬・生活衛生局 医薬安全対策課長 中井 清人 様

厚生労働省 医薬・生活衛生局 医薬品審査管理課長 吉田 易範 様

公益社団法人 日本精神神経学会

理事長 神庭 重信

一般社団法人 日本臨床精神神経薬理学会

理事長 染矢 俊幸

一般社団法人 日本神経精神薬理学会

理事長 中込 和幸

日本統合失調症学会

理事長 福田 正人

外出自粛要請またはロックダウン指示発動時におけるクロザピン検査間隔に関する
緊急対応の要望

【要旨】

新型コロナウイルス感染症の拡大に伴い、医療機関を訪問する行為自体が地域の患者にとって市中感染および院内感染のリスクとなることから、クロザピンによる治療中の患者が一定の条件を満たした場合に、血液モニタリングの検査間隔の延長を要望する。なお、本提言は新型コロナウイルス感染症に関連した緊急時の対応であり、都道府県知事による外出自粛要請、またはロックダウン指示が発動された場合のみ適用する。

【背景】

貴殿らにおかれましては、日頃より精神医療について、ご理解とご尽力をいただき、ありがとうございます。

新型コロナウイルス感染症の拡大に伴い、政府により特別措置法に基づく緊急事態宣言後、都道府県知事による外出自粛要請、またはロックダウン指示が発動される可能性があります。クロザピンは、治療抵抗性統合失調症に唯一適応のある抗精神病薬ですが、現在のところ、本邦ではクロザリル患者モニタリングサービス（CPMS）システムにおいて、無顆粒球症・顆粒球減少症に対応した血液モニタリングが導入され、最長でも 2 週間ごとの白血

球値及び顆粒球値の検査が必要とされています。この検査間隔は諸外国と比較して最も安全性に配慮した基準で導入されました。一方で、医療機関を訪問する行為そのものが、市中感染および院内感染による新型コロナウイルス感染症に罹患するリスクを上昇させます。クロザピンによる無顆粒球症・顆粒球減少症は治療開始後 18 週間に多く、その後有意に減少します。そこで、英国のキングス・カレッジ・ロンドン精神医学研究所およびモーズレイ病院（以下、英国精神医学研究所）では緊急事態宣言発令後、一定の要件を満たした場合、検査間隔を最長 12 週間に延長し、患者が新型コロナウイルスに曝露する機会を減らす取り組みを実施しています（参考資料 1）。

【英国精神医学研究所の対応】

次の条件を満たす場合、表 1 の通り、検査間隔の延長を認める。

- (1) 過去に顆粒球が 2000/microL を下回ったことがない
- (2) 登録した診療機関への安全な訪問が困難
- (3) クロザピン治療を中断すると症状増悪の可能性が高い。

表 1 英国精神医学研究所における緊急事態宣言下の検査間隔

クロザピンによる治療期間	従来の検査間隔	緊急事態宣言下の検査間隔
1-18 週	最長 7 日	最長 14 日
19-52 週	最長 14 日	最長 21 日
>52 週	最長 28 日	最長 84 日

英国における従来の検査間隔は、本邦の CPMS システムの検査間隔と異なるため、同一の基準による同一の対応の導入は議論の余地があります。一方で、新型コロナウイルス感染症が拡大し、危機的状況を迎えた際に、医療機関受診に伴う市中感染および院内感染による新型コロナウイルス感染症に罹患するリスクを可能な限り低減するために、本邦においても同様の取り組みが望ましいと考え、下記の通り提言します。

【提言】

クロザピンによる治療中の患者に対し、次の条件を満たす場合、表 2 の通り検査間隔の延長を認める。

- (1) 政府により特別措置法に基づく緊急事態宣言後、患者の居住する都道府県もしくは登録した診療機関が所在する都道府県の知事による外出自粛要請、またはロックダウン指示が発動されている

- (2) 過去に顆粒球が 2000/microL を下回ったことがない
- (3) 登録した診療機関への安全な訪問が困難
- (4) クロザピン治療を中断すると症状増悪の可能性が高い

表 2 本提言における緊急事態宣言下の検査間隔

クロザピンによる治療期間	従来の検査間隔	緊急事態宣言下の検査間隔
1-26 週	最長 7 日	最長 14 日
26-52 週	最長 14 日	最長 21 日
>52 週	最長 14 日	最長 42 日

ただし、本邦では導入から 18 週間までは原則入院となっていることから、入院患者については従来の検査間隔で採血を行う。

【根拠】

クロザピンによる無顆粒球症・顆粒球減少症は治療開始後 18 週間に多く、その後有意に減少し、特に 52 週以降は無顆粒球症・好中球減少症の新規発症が稀となる（Munro et al. British Journal of Psychiatry 1999）。そこで、52 週より長い期間、顆粒球が 2000/microL を下回ることなく、クロザリルを安全に使用できている症例に対しては、新型コロナウイルス感染症に罹患するリスクを軽減するために、検査間隔を大幅に延長する。ただし、本邦における通常の検査間隔は最長 14 日、つまり英国の検査間隔の半分であることを鑑み、延長する検査間隔も半分の最長 42 日までとする。また、治療期間が 52 週以下の症例に対しては、英国精神医学研究所の対応と同様に 1 週間の延長を認める。ただし、治療期間が 18 週以下の症例では、本邦では原則入院となることから、従来の検査間隔で採血を行う。

【本提言に伴うメリット】

新型コロナウイルス感染症が拡大し、危機的状況を迎えた際に、医療機関受診に伴う市中感染および院内感染による新型コロナウイルス感染症に罹患するリスクを可能な限り低減することが出来る。クロザピン内服中の患者は、一般的に肺炎とそれに伴う死亡リスクが高く（de Leon et al. World Psychiatry 2020）、新型コロナウイルス感染症の重症化と関連するリスク因子（身体合併症、肥満、喫煙歴など）を有する頻度も高いことから、特に新型コロナウイルスに曝露する機会を減らすことが重要な集団と考えられる。

【本提言に伴うリスク】

クロザピンによる無顆粒球症・顆粒球減少症は治療開始後 18 週間に多く、その後有意に減少するため、そのリスクは医療機関受診に伴う市中感染および院内感染による新型コロナウイルス感染症に罹患するリスクより小さいと考える。また、治療期間が 18 週間以下の症例については本邦では原則入院となり、従来の検査間隔で採血が実施されることから、本提言に伴うリスクは非常に小さいと考えられる。

以上

Coronavirus (COVID-19)

Request for extension of clozapine blood test validity

The spread of the coronavirus presents varied problems for healthcare systems. We anticipate that normal monitoring of full blood counts for clozapine patients may be disrupted. Clinicians are invited to request permission (using this form) to extend blood test validity for individual patients in circumstances where clozapine might normally be withheld pending results of a full blood count. A local panel of experts in clozapine use will review the request and respond with 48 hours.

The duration of validity of FBC results depends on the length of time a patient has been treated with clozapine. The amount of clozapine dispensed reflects the validity of this blood test; usually this is 7 days for patients on weekly FBC monitoring, 14 days for patients on fortnightly monitoring, and 28 days for those on 4 weekly monitoring.

Ztas (the clozapine monitoring service for Zaponex) allow for extra supply beyond this blood test validity – an extra 7 days for those on weekly and fortnightly monitoring, and 14 days for those on 4 weekly monitoring. See table below.

Duration of treatment	Monitoring frequency	Maximum Zaponex supply
1-18 weeks	Weekly	14 days
19-52 weeks	Fortnightly	21 days
> 52 weeks	4-Weekly	42 days

Centralised monitoring of leucocyte and neutrophil counts for patients taking clozapine is mandatory. The frequency of blood testing, and therefore duration for which a blood test is considered 'valid', is based on the risk of clozapine-induced neutropenia and agranulocytosis. Dispensing or administering clozapine outside these durations (i.e. without a valid FBC) is unlicensed. The risk of clozapine-induced neutropenia or agranulocytosis is highest in the first 18 weeks of treatment and reduces significantly from then on. Agranulocytosis can lead to fatal sepsis.

A decision to supply clozapine outside the licensed duration of a valid blood test may be taken to meet the needs of a specific patient. The reasons for doing so should be fully explained to the patient and documented in the patient notes.

Requests for extension of blood test validity should be sent to david.taylor@slam.nhs.uk using the attached form.

Request for extension of clozapine blood test validity

Please complete as fully as possible

Patient name:

Date of birth:

NHS number:

Ethnicity:

Diagnosis:

Current medication (please list all, with doses, frequencies and formulation):

Medication	Dose	Frequency	Formulation

Current clozapine treatment

Start date on clozapine:

Due date of next blood test:

Frequency of monitoring:

Expected treatment gap

Reason for expected treatment gap (i.e. explain why testing cannot be performed at the right time):

Anticipated duration of treatment gap (i.e. when can a blood test reasonably be expected to be collected):

Expected clinical consequence of a treatment gap:

Prior clozapine treatment

Please provide details of abnormal FBC results for this patient in any prior episodes of clozapine treatment

Comorbidities

Comorbid medical history:

Benign Ethnic Neutropenia Y/N

Professor David Taylor, Director of Pharmacy

March 18th 2020

Clozapine

Emergency protocol for:

Patients on monthly monitoring

If clozapine patients meet the following criteria:

- Have been on clozapine continuously for more than one year, and
- have not had an ANC $<2000/\mu\text{l}$ (or $<1500/\mu\text{l}$ if they have a history of benign ethnic neutropenia), and
- there is no safe or practical access to neutrophil testing, and
- there is a high risk of deterioration if interruption of clozapine therapy were to occur

then clozapine may be dispensed in the absence of a recent (within 42 days) neutrophil count.

In these patients, a neutrophil count should be done at least every 12 weeks.

Dispensing of greater than the 42-day maximum supply may be warranted if there is a likelihood of there being difficulty in accessing a regular supply of clozapine. The maximum dispensed should be 12 weeks.

In effect, the validity of the FBC is now extended to 12 weeks, allowing a maximum supply of 12 weeks from the date of the last 'green' FBC result.

For people on clozapine with symptoms of infection, including fever, sore throat and flu-like symptoms, an urgent neutrophil count is strongly recommended.

Please note, dispensing of clozapine in the absence of an FBC from the past 42 days is outside the limits of clozapine's Product Licence. The manufacturer accepts no responsibility for this out-of-licence use.

Professor David Taylor
Director of Pharmacy

23rd March 2020

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/340413645>

Consensus statement on the use of clozapine during the COVID-19 pandemic

Article in *Journal of psychiatry & neuroscience: JPN* · April 2020

DOI: 10.1503/jpn.200061

CITATIONS

0

Some of the authors of this publication are also working on these related projects:



Clozapine Covid [View project](#)

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Published online on April 3, 2020; subject to revision

Consensus statement on the use of clozapine during the COVID-19 pandemic

Dan Siskind, MBBS, PhD; William G. Honer, MD; Scott Clark, MBBS, PhD; Christoph U. Correll, MD; Alkomiet Hasan, MD; Oliver Howes, MD, PhD; John M. Kane, MD; Deanna L. Kelly, PharmD; Robert Laitman, MD; Jimmy Lee, MBBS, MMed; James H. MacCabe, MD, PhD; Nick Myles, MD; Jimmi Nielsen, MD, PhD; Peter F. Schulte, MD, PhD; David Taylor, PhD; Helene Verdoux, MD, PhD; Amanda Wheeler, PhD; Oliver Freudenreich, MD

With the ongoing coronavirus disease 2019 (COVID-19) pandemic, psychiatrists find themselves in the clinical situation of being asked by patients, family members and patient advocacy societies to help ensure access to clozapine as a medication critical for ongoing patient care. To provide clozapine prescribing guidance and facilitate regulatory agencies modifying laboratory monitoring and/or dispensing requirements, an expert advisory subgroup of the Treatment Response and Resistance in Psychosis working group developed the following background, recommendations and rationale as a consensus statement.

Clozapine is the most effective antipsychotic for reducing positive symptoms, hospital admissions and all-cause mortality in patients with treatment-refractory schizophrenia.^{1–3} Owing to the risk of clozapine-associated severe neutropenia, absolute neutrophil count (ANC) monitoring programs are a prerequisite for clozapine dispensation in most jurisdictions globally.^{4,5} Region-specific limits on outings and clinical resource constraints during the COVID-19 pandemic may create challenges for patients to access routine clozapine-associated care, including ANC testing required for dispensing. Discontinuing clozapine, especially abruptly, creates significant risk of relapse or exacerbation of severity of illness and needs to be avoided. Given

the importance of continued access to clozapine, for the duration of the public health emergency we recommend the following.

Recommendation 1

The frequency of ANC may be reduced to every 3 months, with dispensation of up to a 90-day supply (if it can be safely stored) for people fulfilling all of the following criteria:

- continuous clozapine treatment for > 1 year
- have never had an ANC < 2000/ μ L (or < 1500/ μ L if history of benign ethnic neutropenia)
- no safe or practical access to ANC testing

Decisions about ANC monitoring for patients on continuous clozapine treatment for 6–12 months may be made on a case-by-case basis. Irrespective of ANC monitoring, patients on clozapine should continue to receive regular clinical assessments of mental state and review of potential adverse drug reactions, either face-to-face or through telehealth consultations. For patients being initiated on clozapine, adherence to current country-specific protocols for ANC monitoring is suggested for the first 6 months of treatment.

Rationale: Maintaining access to routine ANC monitoring for all patients prescribed clozapine is preferred. However, severe neutropenia (ANC < 500/ μ L) is rare (9/1000 people started on clozapine), with a case fatality rate of 2.1%.⁴ Importantly, severe neutropenia has its peak incidence in the first months after clozapine commencement and declines to negligible levels after 1 year.⁴

Recommendation 2

For patients on clozapine with any symptoms of infection (including those reported for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], such as cough, fever and chills, sore throat or other flu-like

symptoms), an urgent physician assessment including a complete blood count (with ANC) should be obtained. The clinical assessment could take place either in person or by telehealth based on local protocols.

Rationale: Clozapine may be associated with a higher risk of pneumonia, likely due to sialorrhea and aspiration rather than neutropenia.⁶ Clozapine-associated neutropenia is thought to occur as a result of selective neutrophil toxicity mediated by clozapine N-oxide metabolites,⁷ or an immune response mediated by a hapten-based mechanism,⁸ both of which occur early in exposure. There is limited information on the impact of coronaviruses on neutrophils among people taking clozapine; however, viral illnesses are generally associated with neutropenia,⁹ and as such severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in some patients may be a cause of neutropenia not etiologically related to clozapine exposure.

Recommendation 3

If patients on clozapine become symptomatic with fever and flu-like symptoms, the emergence of signs and symptoms of clozapine toxicity may require clinicians to reduce the dose of clozapine by as much as a half. Continue the lower dose until 3 days after the fever has subsided, then increase clozapine in a stepwise manner to the pre-fever dose. Where available, clozapine levels help facilitate clinical decision-making, particularly after substantial dosage change, inadequate response or unexpected adverse effects.

Rationale: Clozapine levels can increase with acute systemic infection,¹⁰ leading to symptoms of acute clozapine toxicity, including sedation, myoclonus and seizures. Patients with respiratory infections in or out of hospital may reduce or cease smoking, also leading to raised clozapine levels.¹¹

Any decisions about changes to clozapine dose and monitoring should be made as part of a well-documented, informed consultation with patients and family/caregivers.

Affiliations: From the Metro South Addiction and Mental Health Service, Brisbane, Australia (Siskind); the University of Queensland, School of Clinical Medicine, Brisbane, Australia (Siskind, Myles); the Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada (Honer); the University of Adelaide, School of Medicine, Adelaide, Australia (Clark, Kane); the The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA (Correll, Kane); the Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA (Correll); Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany (Correll); the Department of Psychiatry, Psychotherapy and Psychosomatics of the University Augsburg, Augsburg, Germany (Hassan); the Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK (Howes, MacCabe); the MRC London Institute of Medical Sciences, Hammersmith Hospital, London, UK (Howes); the Institute of Clinical Sciences (ICS), Faculty of Medicine, Imperial College London, London, UK (Howes); the Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA (Kelly); the Bronx Westchester Medical Group, New York, NY, USA (Laitman); the North Region & Department of Psychosis, Institute of Mental Health, Singapore (Lee); the Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore (Lee); the Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen (Nielsen); the Mental Health Service Noord-Holland-Noord, Alkmaar, The Netherlands (Schulte); the South London and Maudsley NHS Foundation Trust, Pharmacy Department, Maudsley Hospital, London, UK (Taylor); the University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Bordeaux, France (Verdoux); the Menzies Health Institute Queensland, Griffith University, Brisbane, Australia (Wheeler); the MGH Schizophrenia Clinical and Research Program, Massachusetts General Hospital, Boston, MA, USA (Freudenreich); and the Harvard Medical School, Boston, MA, USA (Freudenreich).

Competing interests: W. Honer has received consulting fees or sat on paid advisory boards for the Canadian Agency for Drugs and Technology in Health, AlphaSights, Guidepoint, In Silico, Translational Life Sciences, Otsuka, Lundbeck and Newron. S. Clark has received an investigator-initiated grant, participated in an advisory and an educational board and received speakers fees from Lundbeck-Otsuka Australia and received an investigator-initiated grant from Janssen-Cilag Australia. He has received speakers fees from Servier Australia. C. Correll has been a consultant and/or advisor to or has received honoraria from Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda and Teva. He has provided expert testimony for Janssen and Otsuka. He served on a data safety monitoring board for Lundbeck, Rovi, Supernus and Teva. He has received grant support from the Berlin Institute of Health, Janssen, the National Institute of Mental Health, Patient Centered Outcomes Research Institute, Takeda and the Thrasher Foundation. He has received royalties from UpToDate and is a stock op-

tion holder of LB Pharma. A. Hasan has been on the advisory boards and has received speaker fees from Janssen, Lundbeck and Otsuka. O. Howes reports receiving speaker fees, participating on advisory boards, and/or receiving investigator-initiated funding from manufacturers of antipsychotics, including clozapine. J. Kane declares consulting fees/honoraria from Acadia, Alkermes, Allergan, Eli Lilly, Forum, Genentech, Dainippon Sumitomo, H. Lundbeck, Intracellular Therapies, Janssen Pharmaceutical, Jazz Pharma, Johnson & Johnson, LB Pharmaceuticals, Merck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda and Teva, as well as grant support from Otsuka, Lundbeck and Janssen. He is also a shareholder in Vanguard Research Group and LB Pharmaceuticals, Inc. D. Kelly has served as a consultant for Lundbeck, HLS Therapeutics and Alkermes, and is a joint holder of a patent for analytical micro-devices for mental health treatment monitoring (US9581536B2). J. MacCabe has received research grants from, and acted as an unpaid consultant to Lundbeck and Saladax Biomedical. D. Taylor has received research funding from Janssen and Sunovion and lecture payments from Janssen, Lundbeck, Otsuka and Recordati. O. Freudenreich has received a grant from Avanir for a clinical trial involving patients taking clozapine and royalties from UpToDate for the entry on clozapine. No other authors declared competing interests.

DOI: 10.1503/jpn.200061

References

1. Siskind D, McCartney L, Goldschlager R et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2016;209:385-92.
2. Land R, Siskind D, McArdle P, et al. The impact of clozapine on hospital use: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2017;135:296-309.
3. Vermeulen JM, van Rooijen G, Van de Kerkhof MPJ et al. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1–12.5 years. *Schizophr Bull* 2019;45:315-29.
4. Myles N, Myles H, Xia S, et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand* 2018;138:101-9.
5. Nielsen J, Young C, Ifteni P, et al. Worldwide differences in regulations of clozapine use. *CNS Drugs* 2016;30:149-61.
6. de Leon J, Sanz EJ, Norén N, et al. Pneumonia may be more frequent and have more fatal outcomes with clozapine than with other second-generation antipsychotics. *World Psychiatry* 2020;19:120.
7. Husain Z, Almeciga I, Delgado JC et al. Increased FasL expression correlates with apoptotic changes in granulocytes cultured with oxidized clozapine. *Toxicol Appl Pharmacol* 2006;214:326-34.
8. Regen F, Herzog I, Hahn E et al. Clozapine-induced agranulocytosis: evidence for an immune-mediated mechanism from a patient-specific in-vitro approach. *Toxicol Appl Pharmacol* 2017;316:10-6.
9. Baranski B, Young N. Hematologic consequences of viral infections. *Hematol Oncol Clin North Am* 1987;1:167-83.
10. Clark SR, Warren NS, Kim G, et al. Elevated clozapine levels associated with infection: a systematic review. *Schizophr Res* 2018;192:50-6.
11. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol* 2001;21:569-74.