事　務　連　絡
令和２年４月 24 日

一般社団法人日本臨床精神神経薬理学会　御中

厚生労働省医薬・生活衛生局医薬安全対策課

「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」について

医薬品の安全対策については、平素から格別の御高配を賜り厚く御礼申し上げます。

今般、別添写しのとおり、ノバルティスファーマ株式会社宛てに発出しましたので、お知らせします。

写

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ノバルティスファーマ株式会社　御中

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「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」について（検討依頼）

平素より医薬品の適正使用について御協力を賜り、ありがとうございます。

今般、新型コロナウイルス感染症の流行を受け、公益社団法人日本精神神経学会その他３学会より、クロザピン（販売名：クロザリル錠 25mg、同錠 100mg）について、「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」が別紙のとおり提出されました。

つきましては、貴社においても当該要望の内容を精査し、患者の安全確保に十分留意した上でクロザリル患者モニタリングサービス（CPMS）を運用されたく、御検討をお願いします。

別紙

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

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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】

新型コロナウィ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ィ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。

新型コロナウィ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・好中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

球値及び好中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ィ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・好中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ィルスに曝露する機会を減らす取り込みを実施しています（参考資料 1 および 2）。

【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）過去に好中球が 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、新型コロナウィ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ィ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外来患者に対し、次の条件を満たす場合、表 2 の通り CPMS における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）過去に好中球が 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

白血球値・好中球値の検査：

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

血糖値・HbA1c の検査：

血糖値検査間隔	従来の検査間隔	緊急事態宣言下の検査間隔
プロトコール A	最長 84 日	最長 84 日
プロトコール B	最長 28 日	最長 42 日
プロトコール C	最長 14 日	最長 42 日

HbA1c 検査間隔	従来の検査間隔	緊急事態宣言下の検査間隔
プロトコール A	最長 84 日	最長 84 日
プロトコール B	最長 28 日	最長 42 日
プロトコール C	最長 28 日	最長 42 日

ただし、入院患者については従来の検査間隔で採血を行う。なお、国や都道府県等による外出自粛要請が解除された場合は従来の検査間隔で採血を行う。

なお、処方医は症例ごとにリスクとベネフィットを慎重かつ十分に評価し、本提言に基づく検査間隔の延長は、処方医の責任において判断される。

【根拠】

クロザピンによる無顆粒球症・好中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、好中球が 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、新型コロナウィ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。

本邦ではプロトコール B および C に該当する患者の血糖値の検査間隔は最長 28 日および 14 日であるが、新型コロナウィ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し、延長する検査間隔を白血球の検査間隔と同じ最長 42 日までとする。米国、英国、カナダなどの諸外国では空腹時血糖を治療開始時、1 ヶ月後、その後は 4-6 ヶ月ごとに測定することを推奨している。これらを踏まえるとリスクある患者（プロトコール B）では採血間隔を半分にして 2-3 か月、リスクの高い患者（プロトコール C）では採血間隔を 4 分の 1 にして 1 -1.5 カ月にすることが臨床的に妥当と考えられ、緊急事態宣言下の検査間隔は極端に長いものではない。さらに、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ることから、クロザピン導入後初期の耐糖能異常については入院環境下での評価が担保されており、この点からも本提言に伴うリスクは小さいと考えられる。

【本提言に伴うメリット】

新型コロナウィ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ィ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）、新型コロナウィ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、特に新型コロナウィ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・好中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ィ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

参考資料１

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/µl (or <1500/µl 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

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

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

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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/μL (or < 1500/μL 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/μL) 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.

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