

Impact of a novel strategy for critical values communication for the management of patients treated with clozapine

Ruth Cano-Corres¹, Siddarta Acebillo^{2,3}, Francesc Campos Barreda¹,
Diego J. Palao^{2,4}, Eugenio Berlanga-Escalera¹

¹ Department of Biochemistry, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain

² Department of Mental Health, Corporació Sanitària Parc Taulí de Sabadell, Barcelona.

Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Barcelona, Spain

³ Department of Mental Health, Parc Taulí Hospital Universitari, I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain

⁴ Centro de Investigación en Red de Salud Mental, CIBERSAM, Madrid, Spain

ARTICLE INFO

Corresponding author:

Dr. Ruth Cano-Corres
ParcTauli 1, CP: 08208
Sabadell, Barcelona
Spain
Phone: 93.745.84.39
E-mail: rcano@tauli.cat

Key words:

clozapine, e-mail, haemogram alterations,
patients' safety, values communication

ABSTRACT

Introduction

Clozapine is an antipsychotic drug used to treat resistant schizophrenia and other disorders. Based on the actual Spanish legislation, patients treated with clozapine must undergo periodical haematological examinations and treatment should be reviewed when the haemogram shows either a leukocyte count of $\leq 3500/\text{mm}^3$ or neutrophil count $< 2000/\text{mm}^3$. An automatic notification system has been developed to optimize patient management and its utility was assessed following the implementation of the new system.

Material and methods

When clozapine (CLO) laboratory test request was made, a reflex complete blood count test was also done. An automatic e-mail was sent by the laboratory information system to the physician when a CLO was ordered and low leukocyte or neutrophil counts were detected, or when a patient with an ordered CLO test did not attend the laboratory for blood drawing.

Results

For patients with haemogram alterations, the time to take clinical action was significantly decreased from 23 to 7 days ($p = 0.02$). Moreover, the adherence to Spanish Agency of Drugs and Sanitary Devices recommendations significantly increased from 45% to 76% ($p = 0.02$). For not attending patients, the days out of control decreased from 29 to 12 days, although it was not statistically significant ($p = 0.06$).

Conclusions

This strategy has allowed the compliance of legal requirements, the improvement of patient safety, and the optimisation of clinical and laboratory procedures.



INTRODUCTION

Clozapine (CLO) is an antipsychotic drug used in resistant schizophrenia, schizophrenia with extrapyramidal symptoms not responding to other drugs, or psychotic symptoms in Parkinson's disease (1-7).

CLO was discovered in 1958, but in 1975 its commercialisation and prescription were detained since some clinical cases of agranulocytosis, patients presenting neutrophil count under $0.5/\text{mm}^3$, were detected (9-10).

Basing on subsequent studies including haematological examinations, the Food and Drug

Administration (FDA) approved its use for resistant schizophrenia in 1990. In Spain, CLO was re-introduced for clinical practice in 1993 under severe regulatory control conditions. All patients treated with CLO must undergo haematological examinations (haemogram cell counts), weekly during the first 18 weeks of treatment and monthly during the lifelong treatment. The AEMPS (Spanish acronym of Spanish Agency of Drugs and Sanitary Devices) (11) defined these conditions, that remain valid at the time of submitting this manuscript.

The AEMPS defines that, if the haemogram shows a leukocyte count less than $3500/\text{mm}^3$ or neutrophil under $2000/\text{mm}^3$, CLO treatment must be reviewed, modifying drug dose or analytic haemogram control frequency (Table 1).

In Spanish population, agranulocytosis is a rare event, but the incidence of neutropenia and leukopenia is estimated to be 3% and 1.3%, respectively (12).

To avoid unnecessary visits, patients receiving CLO and attending our hospital are first directed to the laboratory for blood drawing for the haemogram analysis and then immediately to the Mental Health Department for a visit with the clinician or a specialised psychiatric nurse.

Upon following the above practice, at the moment of the clinical visit the haemogram results (leukocyte/ mm^3 and neutrophil/ mm^3) are not yet available and can't be reviewed by psychiatric professionals, delaying therapeutic measures for patients presenting with a leukocyte count of less than $3500/\text{mm}^3$ or neutrophil count of under $2000/\text{mm}^3$.

Given the implication to patient safety, developing a good laboratory result communication strategy is essential for clinical practice. A critical result involving therapeutic modifications must be immediately informed to the physicians to ensure the best patient management, avoiding unnecessary treatments or examinations.

Some international organisations have published guidelines and recommendations to ensure the appropriate information communication between the laboratory and clinical departments, like the Joint Commission on Accreditation of Health Care Organization (JCAHO) (13) for laboratory accreditation in the USA, or the Clinical and Laboratory Standards Institute (CLSI) (14) in Europe.

Employing automated rules ensures the detection of 100% of the values requiring immediate communication, minimize human errors and significantly reduce the time to communicate with the physicians, which in turn can prioritize patient visits and results in an overall circuit optimization.

In Spain, some studies have demonstrated that communicated values via e-mail only comprise 1% of all the communications (15), and was a novelty for our hospital.

In May 2018, our clinical laboratory implemented a new laboratory information system (LIS), which made it possible to create informatics algorithms to send an automatic e-mail when certain predefined criteria were met.

This strategy was first applied to patients treated with CLO for automatic notification of altered haematological values, and patients not attending the laboratory. The purpose of this study was to evaluate the impact of a new automatic notification system employing informatics algorithms and e-mails in the clinical management of patients treated with CLO.

MATERIALS AND METHODS

The new LIS employed by the laboratory was Smartlis (Lab Technologies S.A.) v46®, which allows implementation of algorithms and information fluxes with the Mental Health Department to develop a novel strategy of communication.

A new laboratory test named “Clozapine patient control” (CLZ) was created. For patients treated with CLO, when CLZ was ordered by psychiatric physicians or nurses, a reflex haemogram test was also done, this could be differentiated from the other haemograms.

Two different algorithms for automatic advice rules were created.

1. Automatic advice rule: leukopenia/neutropenia detected in a patient treated with CLO

The rule was configured to send an automatic e-mail when the following conditions were met: CLZ test ordered, and leukocyte count $\leq 3500/\text{mm}^3$ or neutrophil count $\leq 2000/\text{mm}^3$.

To assure a quick response e-mails are sent to the physician or nurse ordering the test and to three psychiatric physicians, three laboratory specialists, and one laboratory secretary. To confirm that information was received by the Mental Health Department, it was established that the first psychiatric physician or nurse reading the e-mail had to respond to the Laboratory and take charge of the case. If after 24 hours there was no answer, laboratory staff should contact the Mental Health Department by phone.

The project began in March 2019 and the e-mail text was: “A leukopenia/neutropenia has been detected in the patient Hxxxx”. To ensure data protection only patient clinical history number was included and the e-mail addresses employed were the corporative ones.

Three months later, the text was modified to include AEMPS recommendations on treatment and analysis frequency modifications, when a leukopenia/neutropenia was detected (Table 1).

Table 1 AEMPS recommendations

Haematological count		Required action
Leukocyte (mm ³)	Neutrophil (mm ³)	
≥ 3.500	≥ 2.000	Continue same clozapine treatment
Between ≥3.000 and ≤3.500	Between ≥1.500 and ≤2.000	Continue same clozapine treatment but haematological analysis every 2 weeks, until stabilisation or increased cellular count
< 3.000	< 1.500	Stop clozapine treatment, and haematological analysis every day until resolution. Monitor possible infections. No re-introduction of the drug

1.1 Evaluation of rule utility

To investigate the utility of this rule the following parameters were registered for each patient treated with CLO when leukopenia/neutropenia was detected:

- AEMPS recommendations followed by the physician/nurse: Yes/No
- Number of days to take a clinical decision

All these parameters were obtained by reviewing patient histories and e-mail accounts.

Data obtained from March to December 2018 (n=11) were compared to those from March to December 2019 (n=17), after implementing the automatic notification.

The difference between AEMPS recommendations fulfilment was compared employing a X^2 test, and the time to take a clinical decision with a U Mann-Whitney test.

Also, during March to December 2019, we calculated the percentage of advices made via mail

from the total of laboratory advices to notify critical results (mail and telephone advices).

1.2. Evaluation of proper CLZ requisition

We also evaluated if CLZ test was properly ordered, reviewing all the haemograms ordered by the Mental Health Department from July to October 2019 (n=1811). When leukopenia/neutropenia was detected, we checked if the corresponding patient was treated with CLO.

2. Automatic advice rule: patient treated with CLO not attending the laboratory for blood analysis

Since many patients treated with CLO were absent at the scheduled follow-up visit (neither laboratory analysis nor psychiatric visit), they remained uncontrolled until the next visit. To reduce the time between follow-up visits, the new advice rule sent an e-mail to the coordinating nurse of the Mental Health Department when a patient did not attend the laboratory for the analysis, and a CLZ test was ordered. Thus,

psychiatric professionals could contact the patient and a new analysis could be rescheduled.

The text of the e-mail was: "Patient Hxxxx who had scheduled an analysis for CLZ on xx-xx-xx, did not come to the laboratory". To evaluate the time without follow-up for these patients, the employed parameter was the number of days without follow-up: data of the follow-up analysis - data on the patient who did not go for laboratory analysis.

In order to assess whether time without follow-up was reduced since this automatic rule was implemented, patients not going to the laboratory for blood-drawing between December 2018 (n=16) and December 2019 (n=35) were evaluated, and the differences in the number of days without follow-up were compared using a U Mann Whitney test. The MedCalc® v 7.2.1.0. statistical program was used for the statistical comparisons.

RESULTS

1. Automatic advice rule: leukopenia/neutropenia detected in a patient treated with CLO

From March to December 2019, 1591 CLZ tests were ordered, and 17 met criteria for e-mail

sending (1.06%). From the 17 communications, only two corresponded to inpatients, and the other 15 corresponded to outpatients.

These 17 advices (e-mails) corresponded to eight patients: one patient presented five mail advices during the study period, one patient three advices, one patient two advices, and the last five patients presented one advice each during the study period.

Three patients were men and five women and the average age was 32.5 years.

1.1. Evaluation of rule utility

Confirmity to the AEMPS recommendations increased significantly from 45% (5/11) for patients in 2018, to 76% (13/17) for patients in 2019 ($p = 0.02$).

Table 2 shows the implemented clinical actions for those patients.

The number of days elapsed until the clinical action was implemented significantly decreased from 23 days in the year 2018 to 7 days in 2019, after the application of the advice ($p = 0.02$).

From March-December 2019, 1.22% (17/1389) from all advices made in our laboratory employed an automatic e-mail.

Table 2 Implemented actions in patients with advice during 2019 and 2018

Action	Number of patients	
	2019	2018
New haematological analysis control until leukocyte/neutrophil count recovery	9	1
Stop clozapine	1	0
New haematological analysis + stop other drugs	2	0
No modifications	5	10

1.2. Evaluation of proper CLZ requisition

From July to October 2019, 1811 haemograms were ordered by Mental Health Department.

We detected 3 leukopenia/neutropenia in patients treated with CLO that were not advised by e-mail because a haemogram instead of a CLZ test was erroneously ordered by the psychiatric physician/nurse. Two corresponded to a patient with a previous notice and the haematological alteration was already known. However, the last one corresponded to a patient without previous haematological disorders, thus the e-mail advising the alteration and the potential danger was not sent.

2. Automatic rule: patient treated with CLO not attending the laboratory for blood-drawing

During December 2019, 215 CLZ tests were requested. Thirty-five patients (16.3%) did not present for blood drawing. All e-mails were sent to alarm them, and 27 were rescheduled within 1 month (77%). In December 2018, 149 patients had an analysis scheduled, 16 did not attend (10.7%), and nine of them presented for analysis within 1 month (56.25%).

The days without follow-up decreased from 29 days in December 2018 to 12 days in December 2019 after implementing the warning rule, although statistical significance was not reached ($p = 0.06$).

DISCUSSION

A quality reporting system is defined as the delivery of correct results to the appropriate clinicians in a time frame that ensures patient safety without overburdening both the clinicians and laboratory team (16).

Communication of critical values and clinically significant results is a Joint Commission patient safety goal (17). Failure in communication can

significantly delay patient management (18), and it continues to be one of the most common contributing factors to the development of adverse events (19). Data available in the literature shows an error rate of 3.5% for all telephone calls made from laboratories (20). For this reason, automated informatics systems facilitating the generation of alerts for information transmission ensure patient safety. However, these strategies are not yet widely employed. In a 2008 survey of critical value reporting, the College of American Pathologist found that only 8.6% of 623 institutions communicate critical values using wireless technologies. (21) In Spain e-mail notifications only comprise 1% of all the communications (15).

These data are comparable to the results of our study, in which 1,22% of the communications is made via e-mail after the implementation of the first advice rule.

In our laboratory, the implementation of a novel LIS enabled the development of an automatic communication system employing informatics algorithms and e-mail to send an alert when some established criteria were met.

For patients presenting haematological alterations, the implementation of the first rule has advanced the application of the required clinical action. Also the compliance of the AEMPS recommendations has significantly increased, although it was not applied for 24% of the cases ($n=4$). In two of the four cases, patients were controlled in another hospital and for the other two cases the clinical specialist evaluated the patient and decided to continue with the treatment and analysis frequency. This automatic strategy also ensured the detection of 100% of haemogram alterations. Some clinical situations, such as bacterial infections, may cause leukocyte count elevations. In these cases, decreases in leukocyte count caused by CLO treatment may be masked. Therefore, these

situations must be taken into account in this type of patients.

As we have reported, most of the advices (85%) were sent to outpatients, who are the most benefited from employing this communication strategy.

It is important to remark that demanding the correct CLZ test is essential for the correct operation of the circuit, to avoid the loss of leukopenia/neutropenia cases detected. In our opinion, for the future, automatic systems which could link patient treatment information with analytical tests ordering could be essential to avoid errors attributed to manual test ordering.

For patients that usually renege on their visits, the second reminder rule reduced the time these patients spent without follow-up. Statistically significant differences were not achieved, maybe due to the high standard deviation observed in both groups and the low number of not attending patients in December 2018. Future studies with higher number of patients would be probably required to find significant differences.

Moreover, the two rules allowed to identify a group of patients defined as “well-controlled patients”: patients without haematological alterations and generally adhering to the visits/analysis. For these patients, the frequency of their visits to the Mental Health Department had been spread and the quality of the clinical visit improved. For instance, during the clinical visits physicians may spend more time giving recommendations for a healthy life and emotional aspects, instead of spending time reviewing laboratory data.

Globally, all patients have benefited from the application of both rules.

For the Mental Health Department, this strategy is supposed to ensure the fulfilment of actual legislation and the improvement of patient

management. The demonstrated benefits of this collaboration should motivate the adoption of similar strategies in many other clinical ambits of our hospital. Many patients treated with other drugs could benefit from this type of warning rules, for example those treated with azathioprine which also cause agranulocytosis.

Some experiences have been published in relation to automated communication, using e-mail or SMS, vs. oral communication. For example, in Spain, an SMS system was implemented to notify microbiological results with many useful benefits, such as the reduction in the time of notification, and elimination of risk errors when there is no repetition of the information received by the recipient to the laboratory staff (22). Another Italian study was performed employing two instant notification systems: the short message service (SMS) and an alert message on the desktop computer (23). Computerised communication demonstrated a reduction in notification time and yielded additional benefits: it eliminated the risk of errors occurring by phone notification and erroneous patient identification and test and value reporting, which occurs if the read-back step is not used.

All studies support the importance of the read-back step, our study established that if no answer were received 24 h after sending the advice e-mail, laboratory staff would contact the Mental Health Department to ensure communication.

Many studies have demonstrated that automatic alerting systems reduce the time until the provision of appropriate treatment in patients with critical laboratory results, showing a reduction of time until the resolution of patient abnormality by 29% (24,25). In our study the reduction of time until a clinical decision was applied was significantly reduced by 67% (22.36 to 7.29) days, showing significant reductions than published data.

CONCLUSION

This strategy has allowed the compliance of legal requirements, the improvement of patient safety, and the optimisation of clinical and laboratory procedures.

REFERENCES

1. Barnes TR. Schizophrenia Consensus Group of British Association Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2011;25:567-620.
2. Mortimer AM, Singh P, Shepherd CJ, Puthiyackal J. Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clin Schizophr Relat Psychoses*. 2010;4:49-55.
3. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373:31-41.
4. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomised controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull*. 2006;32:715-23.
5. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al., CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163:600-10.
6. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60:553-64.
7. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic, A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789-96.
8. Hippus H. A historical perspective of clozapine. *J Clin Psychiatry*. 1999;60 Suppl 12:S22-3.
9. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. Clozapine and agranulocytosis. *Lancet*. 1975; 2(7935): 611.
10. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: A situation report up to August 1976. *Eur J Clin Pharmacol*. 1977;11:199-201.
11. Dirección General de Farmacia y Productos Sanitarios. Circular nº 10/93 sobre reglamentación específica para la prescripción, dispensación y utilización de leponex. Madrid: Ministerio de Sanidad y Consumo; 1993. Available at: <http://www.ub.edu/legmh/disposici/cir1093.htm>.
12. Pons A, Undurraga J, Batalla A, Beranrdo M. Clozapina y agranulocitosis en España: ¿tenemos una población más segura? Seguimiento hematológico a 5 años de una cohorte de pacientes tratados con Clozapina. *Rev Psiquiatr Salud Ment (Barc.)*. 2012;5:37-42
13. Joint Commission on the Accreditation of Healthcare Organisations: National Patient Safety Goals. Available at: <https://www.jointcommission.org/standards/national-patient-safety-goals/>.
14. Clinical and Laboratory Standards Institute (CLSI), Management of Critical- and Significant-risk Results 1st Edition CLSI Guideline GP47 950 West Valley Road, Suite 2500, Wayne, PA 19087, (2015).
15. María Antonia Llopis Díaz, Rubén Gómez Rioja, Virtudes Álvarez Funes, Cecilia Martínez Brú, Mariano Cortés Rius, Nuria Barba Meseguer, Montse Ventura Alemany y María Jesús Alsina Kirchner. Comunicación de valores críticos: resultados de una encuesta realizada por la comisión de la calidad extraanalítica de la SEQC-ML. *Rev Lab Clin*. 2010;3:177-182
16. Piva E, Plebani M. Interpretative reports and critical values. *Clin Chim Acta*. 2009;404:52-8.
17. Joint Commission. National Patient Safety Goals, 2013. http://www.jointcommission.org/standards_information/npsgs.aspx.
18. Singh H, Arora HS, Vij MS, et al. Communication outcomes of critical imaging results in a computerised notification system. *J Am Med Inform Assoc* 2007;14:459-66.
19. Emancipator K. Critical values: ASCP practice parameter: American Society of Clinical Pathologists. *Am J Clin Pathol*. 1997;108:247-253.
20. Barenfanger J, Sautter RL, Lang DL, et al. Improving patient safety by repeating (read-back) telephone reports of critical information. *Am J Clin Pathol*. 2004;121:801-803.
21. Dighe AS, Jones JB, Parham S, et al. Survey of critical value reporting and reduction of false-positive critical value results. *Arch Pathol Lab Med*. 2008;132:1666-1671.
22. A.F. Guzman, et al. Utilización de la Historia Digital de Salud y la aplicación "WebMovil" corporativa en la gestión de la comunicación de resultados críticos de Microbiología, en el ámbito de Atención Primaria de un Área Sanitaria. *Rev Esp Quimioter* 2014;27: 36-42
23. Piva E1, Sciacovelli L, Zaninotto M, Laposata M, Plebani M. Evaluation of effectiveness of a computerised notification system for reporting critical values. *Am J Clin Pathol*. 2009 Mar;131(3):432-41. doi: 10.1309/AJCPYS80BUCBXTUH.

24. Kuperman G, Sittig DF, Shabot M, et al. Clinical decision support for hospital and critical care. *J Healthc Inf Manage.* 1999;13:81-96.

25. Kuperman GJ, Teich JM, Tanasijevic MJ, et al. Improving response to critical laboratory results with automation: results of a randomised controlled trial. *J Am Med Inform Assoc.* 1999;6:512-522.