Blood Draw Barriers for Treatment with Clozapine and Development of Point-of-Care Monitoring Device

Article *in* Clinical Schizophrenia & Related Psychoses · April 2015

DOI: 10.3371/CSRP.KEBE.070415

CITATIONS
2

READS
58

15 authors, including:

Hadar Ben-Yoav
Ben-Gurion University of the Negev
59 PUBLICATIONS **377** CITATIONS
SEE PROFILE

Thomas E. Winkler
KTH Royal Institute of Technology
28 PUBLICATIONS **86** CITATIONS
SEE PROFILE

Eunkyoung Kim
University of Maryland, College Park
62 PUBLICATIONS **681** CITATIONS
SEE PROFILE

Robert P Mcmahon
University of Maryland, Baltimore
248 PUBLICATIONS **9,457** CITATIONS
SEE PROFILE

CLINICAL SCHIZOPHRENIA & RELATED PSYCHOSES

Rapid Electronic Article in Press

DOI: 10.3371/CSRP.KEBE.070415

Blood Draw Barriers for Treatment with Clozapine and Development of Point-of-Care Monitoring Device

Deanna L. Kelly [a,*,+], Hadar Ben-Yoav [b,c,*], Gregory F. Payne [d,e], Thomas E. Winkler [b,d], Sheryl E. Chocron [b,d], Eunkyoung Kim [e], Veronika Stock [a], Gopal Vyas [a], Raymond C. Love [f], Heidi J. Wehring [a], Kelli M. Sullivan [a], Stephanie Feldman [a], Fang Liu [a], Robert P. McMahon [a], Reza Ghodssi [b,c,d,+]

* Share first authorship

[a] Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland 21228, United States.

[b] MEMS Sensors and Actuators Laboratory (MSAL), University of Maryland, College Park, Maryland 20742, United States.

[c] Department of Electrical and Computer Engineering, Institute for Systems Research, University of Maryland, College Park, Maryland 20742, United States.

[d] Fischell Department of Bioengineering, University of Maryland, College Park, Maryland 20742, United States.

[e] Institute for Bioscience and Biotechnology Research, University of Maryland, College Park, Maryland 20742, United States.

[f] University of Maryland School of Pharmacy, Baltimore, Maryland 21201, United States.

[+] Corresponding authors:

Deanna L. Kelly:

Present postal address:

Maryland Psychiatric Research Center

University of Maryland School of Medicine

Baltimore, MD 21228

United States

Telephone number: +1 (410) 402-6861

Fax number: +1 (410) 402-6880

E-mail address: dkelly@mprc.umaryland.edu

Reza Ghodssi:

Present postal address:

Institute for Systems Research

Department of Electrical and Computer Engineering

University of Maryland

College Park, MD 20742

United States

Telephone number: +1 (301) 405-8158

Fax number: +1 (301) 314-9920

E-mail address: ghodssi@umd.edu

Abstract

Background: Clozapine is the most effective antipsychotic drug for schizophrenia treatment, however it is currently underused. In order to understand the barriers of frequent blood draws for white blood cell counts (WBCs) and clozapine levels, we developed a psychiatrist survey and began and integrative approach of designing a point-of-care device that could eventually have real-time monitoring with immediate results. **Methods:** We ascertained barriers related to clozapine management and the acceptance of possible solutions by sending an anonymous survey to physicians in psychiatric practice (N=860). In parallel we tested clozapine sensing using a prototype point-of-care monitoring device. **Results:** 255 responses were included in the survey results. The two barriers receiving mean scores with the highest agreement as being a significant barrier were patient nonadherence to blood work and blood work's burden on the patient (out of 28). Among nine solutions, the ability to obtain lab results in the physician's office or pharmacy was top-ranked (mean±sd Likert scale (4.0±1.0)). Physicians responded that a point-of-care device to measure blood levels and WBCs would improve care and increase clozapine use. Residents ranked point-of-care devices higher than older physicians (4.07±0.87 vs. 3.47±1.08, $p<0.0001$). Also, the prototype device was able to detect CLZ reliably in 1.6, 8.2, and 16.3μg/mL buffered solutions. **Discussion:** Survey results demonstrate the physician's desire for point-of-care monitoring technology, particularly among younger prescribers. Prototype sensor results identify that clozapine can be detected and integrated for future device development. Future development will also include integration of WBCs for a complete detection device.

Keywords: Clozapine; Antipsychotic; Medication underutilization; Sensing lab-on-a-chip; Point-of-care; Therapeutic Drug Monitoring (TDM)

1. Introduction

Schizophrenia is one of the most challenging and complex psychiatric disorders that afflicts humans. It is a devastating illness that affects 1% of the population worldwide. The burden of the disorder is high with the estimated direct and indirect costs of the illness (2002 figures) exceeding $60 billion annually (1). Currently there is no cure for the disorder and lifelong treatment with antipsychotics is recommended (2). Clozapine (CLZ) is the most effective antipsychotic treatment for chronic and treatment refractory patients with schizophrenia. It is the only antipsychotic that has been FDA-approved for treatment-resistant schizophrenia and it provides effective treatment even when patients do not respond to other second-generation antipsychotics (3). No existing first or second-generation antipsychotic is as effective as CLZ monotherapy in treatment-resistant patients (2, 4-7).

Current evidence-based pharmacologic guidelines for the treatment of schizophrenia recommend prescribing CLZ for individuals who are unresponsive or partially responsive to first line medications, which is up to 40% of patients with schizophrenia (8). Despite the overwhelming evidence of the superior effectiveness of CLZ compared to other antipsychotics in treatment-resistant schizophrenia, prescription rates for CLZ in the U.S. are far lower than the estimated prevalence of treatment-resistant schizophrenia (9-12). There are many possible barriers to using CLZ and a few reports have noted the most significant barriers to be the registration process, tolerability and side effects, and nonadherence to blood draws (13, 14). Also, lack of education and experience with CLZ serves as a barrier as psychiatrists have been reported to overestimate the actual risk of agranulocytosis (15) and underestimate how well patients like taking it (16),

One of the most frequently identified barriers known is the issue around frequent bloodwork needed to effectively manage this medication. In current practice, CLZ patients have many blood draws to monitor white blood cell (WBC) counts for agranulocytosis, a rare but potentially fatal side effect. Since WBCs need to be monitored weekly for six months, the addition of separate blood draws to measure CLZ

levels involves considerable inconvenience to the patient on a weekly basis. CLZ is the only antipsychotic whose efficacy has been predicted by blood measurement (17-22). In addition, the Schizophrenia Patient Outcomes Research Team (PORT) guidelines recommend that blood level monitoring be performed to aim for optimal therapeutic response (2). Blood levels can also help in identifying medication nonadherence which is a widespread problem in people with psychiatric disorders, as nonadherence can make it more difficult to re-achieve a response on relapse (23) and nonadherence is associated relapse and possibility for hospitalization or even suicide (24, 25). Blood levels provide important guidance during acute illness and changes in smoking patterns that could lead to large fluctuations both high and low leading to relapse or toxicity (26-32). However, currently despite these blood draws as standard of care, they are frequently overlooked (2) or due to the lag time of results and the infrequent psychiatry visits, the utility is often less limited than ideal.

We hypothesized that among many barriers to care, better ways to monitor real-time treatment with CLZ could make this medication more acceptable and widely utilized. Thus, we developed a survey for psychiatrists to better understand the impact of blood work and other barriers on CLZ use. At the same time we began a collaboration between the School of Medicine and the Department of Engineering to begin to test and develop ways to provide technology as a solution to monitoring of CLZ (33). The research plan was to also ascertain how psychiatrists feel about technological aids for to help with blood draws. In particular we focused on point of care (POC) monitoring devices. POC testing devices are based on lab-on-a-chip (LOC) sensing micro-systems that provide numerous advantages in clinical diagnostics, environmental monitoring, and biomedical research fields (34-38). The ideal LOC will combine the ability to provide real time monitoring of WBC and CLZ levels to the physicians with minimal invasiveness and immediate results. Here we focus on the novel development of technology to detect the CLZ levels. Technology for WBC detection is available and other techniques by our group is currently also under development but not the focus of this paper. Others have reported that using types of POC devices for hematological monitoring and patients with schizophrenia feel less discomfort and inconvenience (39). Our group along with many schizophrenia treatment experts believe that CLZ is

grossly underutilized in the U.S. and improving acceptability and accessibility could significantly improve outcomes for schizophrenia patients (10-12, 40-46). This paper presents barriers and identifies one advancement that may help improve outcomes of people in need of CLZ treatment.

2. Methods

Questionnaire survey

We prepared an anonymous survey questionnaire sent to psychiatrists (psychiatry residents, fellows, psychiatrists) in the State of Maryland. This survey asked a series of questions on a 5 point Likert Scale (1 = strongly disagree, 5 = strongly agree) regarding the barriers related to CLZ use, blood draw issues with CLZ, and the physician's interest and willingness to use novel technology and point of care devices to monitor CLZ. In addition, the survey solicited the physician's willingness to increase the utilization of CLZ if LOC technology was available. This survey was sent to 860 physicians in the state of Maryland and response was anonymously returned by mail or Survey Monkey®. Respondents were recruited from different settings including University of Maryland and Medical System and affiliates, Department of Health and Mental Hygiene State facilities, the Sheppard Pratt Health System, through direct research of community facilities and prescribers, and through the Maryland Psychiatric Society. The survey consisted of 56 questions: 12 demographic, 28 related to barrier perception, 9 related to solutions; 6 related to a POC device, 1 open ended text. Here we report on data related to the POC device and blood draws primarily (47, 48). The anonymous protocol was determined exempt by the University of Maryland and the Department of Health and Mental Hygiene Institutional Review Boards

Lab-on-a-chip sensor for clozapine detection

Following the results of the survey from physicians we developed a prototype for a POC LOC sensor to detect CLZ. This was performed between a collaboration of investigators from the University of Maryland – Baltimore and College Park campuses (Maryland Psychiatric Research Center and the Institute for Systems Research at the School of Engineering). The integrated LOC device is composed

of 2 components (Figure 1): a sensor (an array of sensor electrodes in the bottom part) and a testing chamber (3 parallel chambers in the top part). Because a bare gold electrode does not produce an adequate signal, we have been testing the amplification of the electrical signal of clozapine using chitosan, a natural polymer, that is compatible with microfabrication (49), modified with a redox material catechol. The resulted catechol-modified chitosan sensor enables CLZ detection through a redox cycling mechanism. The grafted catechol moieties in the redox cycling system can participate in an electron transfer reaction and be inter-converted between oxidized (Q) and reduced (QH_2) forms (E_0 = +0.2 V). CLZ (E_0 = +0.4 V) is an electro-active species that can diffuse freely within the chitosan film. Upon the application of voltage values higher than its E_0 (overpotential conditions), CLZ is oxidized, followed by its reduction by the grafted QH_2 moieties, and re-oxidation at the electrode (Figure 2a and 2c). This continuous CLZ reduction/oxidation cycle results from this use of CLZ as an oxidizing mediator (Figure 2b). With such continuous redox reaction we hypothesize that the total charge transferred by CLZ oxidation is increased, amplifying the generated electrochemical current and improving the signal-to-noise ratio. Redox cycling system recovering to the reduced state is achieved by the application of negative potential in the presence of a reducing mediator, hexaammineruthenium(III) (HARu, E_0 = −0.2 V of $Ru^{2+/3+}$ reaction).

All chemicals were purchased from Sigma-Aldrich. All chemical testing solutions were prepared in phosphate buffer (PB; 0.1 M, pH 7). The electrochemical characterization technique cyclic voltammetry was used to record CLZ sensing signals (range of −0.4 V to +0.7 V, scan rate of 0.02 V/s, scan resolution of 0.001 V). Background signals were similarly recorded using buffered solution with only 25 μM HARu. All electrochemical tests were carried out using a CHI660D single channel potentiostat from CH Instruments (Austin, TX). All voltages were denoted versus the relevant reference electrode half-cell potential. The initial establishment of the feasibility to detect CLZ was tested with buffer solutions containing various concentrations of CLZ. See supplementary information for a full description of the sensor development and optimization.

3. Results

Questionnaire survey

We sent out 860 surveys and received back 277 (32% response). Two-hundred fifty five surveys were included in the final analyses as 16 were incomplete and 6 respondents declined stating they didn't feel they could adequately respond. Table 1 lists the demographic features of the survey respondents. Among 28 listed barriers (clinical, nonclinical and side effects) to more frequent use of CLZ, the two that ranked highest were: 1) Patients will likely be non-adherent to blood work (score 3.7 ± 1.1) and 2) The burden of blood work on the patient (score 3.6 ± 1.2) (Table 2). Also, among nine potential solutions for increased CLZ use, CLZ levels and WBC measurement in the physician office or pharmacy was top ranked (4.0 ± 1.0). Physicians agreed that a POC device would improve care and that it would increase their CLZ use with a mean score of 3.9 ± 1.0.

Agreement ratings were significantly higher for residents compared to older physicians, suggesting that residents are eager to use technology to improve patient care (4.07 ± 0.87 vs. 3.47 ± 1.08; $t = 3.40$, $df = 340$, $p < 0.0001$)). Among the types of devices suggested, 59% of physicians ranked a handheld device as the preferred monitoring modality. Among residents and younger physicians, 73% preferred a handheld device to monitor CLZ treatment (47).

Clozapine detection with the lab-on-a-chip sensor

. The electrochemical signal of CLZ was recorded in the presence and absence of the catechol-modified chitosan system and the results are presented in figure 3. An anodic current density peak at an electric potential of +0.4 V, as expected due to CLZ oxidation reaction, showed the amplification effect. A signal 2.5-fold higher compared to an unmodified bare electrode was determined, which is close to our previously determined 3-fold for millimeter-scale electrodes (33).

The detection feasibility of 5 (1.6 μg/mL), 25 (8.2 μg/mL), and 50 (16.3 μg/mL) μM CLZ in buffered micro-liter solutions with the microelectrodes is shown in figure 4. The calculated total oxidative charge generated between 0 and +0.7 V in the measured cyclic voltammograms reveals a positive CLZ dose-

dependence. These results provide initial promise as the first step towards the development of a POC testing device based on a microfluidic LOC for CLZ detection.

4. Discussion

Here we presented an integrated approach to develop an engineered medical solution for CLZ treatment management. By understating the barriers and identifying the technological needs, new paradigms will be established and will help designing innovative and effective solutions. The results of this study demonstrate the need for POC testing technology, particularly among younger prescribers. Psychiatrists feel their use of CLZ is hindered by frequent blood draws and welcome technology that could advance the ease of sensing CLZ and WBC blood levels. In fact our study shows that nonadherence to blood work is the top rated barrier by practicing psychiatrists in the State of Maryland. Furthermore, the top rated solution for improving CLZ use was the use of POC monitoring devices. We realize there are many barriers to care and many aspects to improve upon but have used this survey as the framework for developing POC technology.

A miniaturized prototype sensor for CLZ detection is developed as a model POC monitoring solution to overcome some of the barriers around blood draws. With this prototype, challenges related to sensor development such as sensitivity and detection limit, as well as compatibility with blood samples and integration of pretreatment steps are identified. In future work, we will focus on defining specific technological requirements for improved sensitivity and better acceptance by users. The next level of a questionnaire will be conducted to evaluate usability factors (*e.g.*, human factors, mode and place of use, and cost) that will impact this developing solution. The detection limit and the dynamic range of the sensor will be characterized in the next steps with relation to the required clinical range. Following performance characterization of the device with serum fluids, a flow system will be integrated to realize a fully autonomous micro-system for clinical monitoring of CLZ blood levels in schizophrenia patients. This device will allow treatment teams to perform analysis at the POC in a low cost, fast, and

straightforward way aiming to guide CLZ dosages within the effective range (21), to decrease the patient's burden, and to personalize medical care. To further reduce the burden of monitoring, we also plan to incorporate WBC monitoring into a fully miniaturized and portable instrument that can return both blood level monitoring and WBC detection in the same unit.

The main challenges that arise within micro-scale systems are the large deviations observed in CLZ detection and the overall lower sensing performance. Accurate control of system biofabrication is critical to overcome these challenges. Therefore, a comprehensive characterization of the microfluidic device architecture (*e.g.*, electrodes and microfluidics geometry), the biofabrication process (*e.g.*, chitosan electrodeposition and catechol grafting steps) and the sensing performance (*e.g.*, sensitivity, selectivity, and compatibility with human serum) will be conducted in future studies to maximize the amplification performance and accuracy of the sensor. The main limitation to the survey was that only about 1/3 of all prescribers sent the surveys responded which may overestimate favor of CLZ use or more motivated prescribers. However, understanding more about the needs and solutions for prescribers is critical and the majority responding think they would benefit and patients would benefit by POC monitoring.

By addressing the need for real time monitoring of blood antipsychotic levels, more rapid results can be available to help guide treatment. This approach could potentially reduce the cost and burden of monitoring, and increase the acceptability of psychiatric drug treatment to patients and prescribers. It will also aid in higher acceptability and treatment response. The incorporation of WBC counts would make a LOC biosensing device attractive for POC use, decreasing costs and patient burden and changing the paradigm of how we currently monitor psychiatric drug treatment. This novel application of LOC monitoring of psychiatric drug treatment can revolutionize and provide a new model for mental health disorder research. It is a first step in personalized medical care that millions of mental health patients could benefit from worldwide.

Acknowledgments:

The authors would like to thank the Robert W. Deutsch Foundation, The Maryland Innovation Initiative (MII), the National Science Foundation Maryland Engineering Research Internship Teams (MERIT) and the NSF Grant No. DGE0750616 for financial support. The authors likewise appreciate the support of the Maryland NanoCenter and its FabLab. The authors wish to also thank the Bioengineering rotation students in MSAL: Bao-Ngoc Nguyen, Bharath Ramaswamy, Stephan Restaino, and Nicholas Woolsey and the undergraduate intern Gillian Costa for the useful discussions.

References:

1. Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of Schizophrenia in the United States in 2002. Journal of Clinical Psychiatry. 2005;66:1122-9. doi: 10.4088/JCP.v66n0906.

2. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 Schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophrenia Bulletin. 2010;36:71-93. doi: 10.1093/schbul/sbp116.

3. Conley RR, Tamminga CA, Kelly DL, Richardson CM. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. Biological Psychiatry. 1999;46:73-7. doi: 10.1016/S0006-3223(99)00029-3.

4. Azorin JM, Spiegel R, Remington G, Vanelle JM, Pere JJ, Giguere M, et al. A double-blind comparative study of Clozapine and Risperidone in the management of severe chronic Schizophrenia. The American Journal of Psychiatry. 2001;158(8):1305-13. PubMed PMID: 11481167.

5. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al. Effects of clozapine on positive and negative symptoms in outpatients with Schizophrenia. American Journal of Psychiatry. 1994;151:20-6.

6. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. a double-blind comparison with Chlorpromazine. Archives of General Psychiatry. 1988;45(9):789-96. PubMed PMID: 3046553.

7. Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, et al. Clozapine, Olanzapine, Risperidone, and Haloperidol in the treatment of patients with chronic Schizophrenia and Schizoaffective Disorder. The American Journal of Psychiatry. 2002;159(2):255-62. PubMed PMID: 11823268.

8. Teo C, Zai C, Borlido C, Tomasetti C, Strauss J, Shinkai T, et al. Analysis of treatment-resistant Schizophrenia and 384 markers from candidate genes. Pharmacogenetics and Genomics. 2012;22(11):807-11. doi: Doi 10.1097/Fpc.0b013e3283586c04. PubMed PMID: ISI:000309977100009.

9. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of Clozapine use in Maryland and in Victoria, Australia. Psychiatric Services. 2005;56:320-3. doi: 10.1176/appi.ps.56.3.320.

10. Lieberman JA. Maximizing Clozapine therapy: managing side effects. Journal of Clinical Psychiatry. 1998;59:38-43.

11. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving Clozapine: a case note review. The Journal of Clinical Psychiatry. 2003;64(1):30-4.

12. Weissman EM. Antipsychotic prescribing practices in the veterans healthcare administration--New York metropolitan region. Schizophrenia Bulletin. 2002;28(1):31-42.

13. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatrica Scandinavia. 2014;130:16-24.

14. NC Division of Mental Health, Developmental Disabilities and Substance Abuse Services and the North Carolina Psychiatric Association; http://naminc.org/nn/0910Conf/clozapineresearch.pdf

15. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrist's attitude towards and knowledge of clozapine treatment. Journal of Psychopharmacology. 2010;24:965-71.

16. Hodge K, Jesperson S. Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians. International Journal of Mental Health Nursing. 2008;17:2-8.

17. Freeman DDJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in Clozapine therapy? Clinical Pharmacokinetics. 1997;32:93-100. doi: 10.2165/00003088-199732020-00001.

18. Haring C, Meise U, Humpel C, Saria A, Fleischhacker WW, Hinterhuber H. Dose-related plasma levels of Clozapine: influence of smoking behaviour, Sex and Age. Psychopharmacology. 1989;99(1):S38-S40. doi: 10.1007/bf00442557.

19. Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY. Relationship between clinical efficacy and Clozapine concentrations in plasma in Schizophrenia: effect of smoking. Journal of Clinical Psychopharmacology. 1993;13(6):383-90.

20. Perry PJ, Bever KA, Arndt S, Combs MD. Relationship between patient variables and plasma Clozapine concentrations: a dosing nomogram. Biological Psychiatry. 1998;44(8):733-8. doi: http://dx.doi.org/10.1016/S0006-3223(97)00531-3.

21. Stark A, Scott J. A review of the use of Clozapine levels to guide treatment and determine cause of death. Australian and New Zealand Journal of Psychiatry. 2012;46:816-25. doi: 10.1177/0004867412438871.

22. Warner B, Alphs L, Schaedelin J, Koestler T. Clozapine and sudden death. The Lancet. 2000;355(9206):842-3.

23. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry. 2008;8:32.

24. Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of Schizophrenia in the United States. Current Medical Research and Opinion. 2007;23:2305-12. doi: 10.1185/030079907X226050.

25. Modai I, Hirschmann S, Rava A, Kurs R, Barak P, Lichtenberg P, et al. Sudden death in patients receiving clozapine treatment: a preliminary investigation. Journal of Clinical Psychopharmacology. 2000;20:325-7.

26. Brownlowe K, Sola C. Clozapine toxicity in smoking cessation and with ciprofloxacin. Psychosomatics. 2008;49:176. doi: 10.1176/appi.psy.49.2.176.

27. Derenne JL, Baldessarini RJ. Clozapine toxicity associated with smoking cessation: case report. American Journal of Therapeutics. 2005;12:469-71.

28. Leung JG, Nelson S, Takala CR, Gören JL. Infection and inflammation leading to clozapine toxicity and intensive care: a case series. Annals Pharmacotherapy. 2014;48:801-5. doi: 10.1177/1060028014526701.

29. Matthews CJ, Hall TL. A clozapine conundrum: clozapine toxicity in an acute medical illness. Australasian Psychiatry. 2014;22:543-5. doi: 10.1177/1039856214559041.

30. Espnes KA, Heimdal KO, Spigset O. A puzzling case of increased serum clozapine levels in a patient with inflammation and infection. Therapeutic Drug Monitoring. 2012;34:489-92. doi: 10.1097/FTD.0b013e3182666c62.

31. Darling P, Huthwaite MA. Infection-associated clozapine toxicity. Clinical Schizophrenia & Related Psychoses. 2011;5:159-60. doi: 10.3371/CSRP.5.3.7.

32. Jecel J, Michel TM, Gutknecht L, Schmidt D, Pfuhlmann B, Jabs BE. Toxic clozapine serum levels during acute urinary tract infection: a case report. European Journal of Clinical Pharmacology. 2005;60:909-10.

33. Ben-Yoav H, Winkler TE, Kim E, Chocron SE, Kelly DL, Payne GF, et al. Redox cycling-based amplifying electrochemical sensor for *in situ* clozapine antipsychotic treatment monitoring. Electrochimica Acta. 2014;130:497-503. doi: 10.1016/j.electacta.2014.03.045.

34. Chin CD, Linder V, Sia SK. Lab-on-a-chip devices for global health: past studies and future opportunities. Lab on a Chip. 2007;7:41-57.

35. Craighead H. Future lab-on-a-chip technologies for interrogating individual molecules. Nature. 2006;442:387-93. doi: 10.1038/nature05061.

36. Figeys D, Pinto D. Lab-on-a-chip: a revolution in biological and medical sciences. Analytical Chemistry. 2000;72(9):330 A-5 A. doi: 10.1021/ac002800y.

37. Mohammed MI, Desmulliez MPY. Lab-on-a-chip based immunosensor principles and technologies for the detection of cardiac biomarkers: a review. Lab on a Chip. 2011;11(4):569-95. doi: 10.1039/c0lc00204f. PubMed PMID: WOS:000286765700001.

38. Weigl BH, Bardell RL, Cabrera CR. Lab-on-a-chip for drug development. Advanced Drug Delivery Reviews. 2003;55:349-77.

39. Nielsen J, Thode D, Stenager E, Andersen KØ, Sondrup U, Hansen TN, et al. Hematological clozapine monitoring with a point of care device: a randomized cross over trial. European Neuropsychopharmacology. 2012;22:401-5.

40. Xiang Y-T, Wang C-Y, Si T-M, Lee EH, He Y-L, Ungvari GS, et al. Clozapine use in Schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. Australian and New Zealand Journal of Psychiatry. 2011;45(11):968-75.

41. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. American Journal of Psychiatry. 2003;160(10):1817-22. doi: DOI 10.1176/appi.ajp.160.10.1817. PubMed PMID: ISI:000185880300018.

42. Kelly DL, Dixon LB, Kreyenbuhl JA, Medoff D, Lehman AF, Love RC, et al. Clozapine utilization and outcomes by race in a public mental health system: 1994-2000. The Journal of Clinical Psychiatry. 2006;67(9):1404-11. Epub 2006/10/05. PubMed PMID: 17017827.

43. Kreyenbuhl J, Valenstein M, McCarthy JF, Ganoczy D, Blow FC. Long-term combination antipsychotitreatment in VA patients with Schizophrenia. Schizophrenia Research. 2006;84(1):90-9.

44. Mallinger JB, Fisher SG, Brown T, Lamberti JS. Racial disparities in the use of second-generation antipsychotics for the treatment of Schizophrenia. Psychiatric Services. 2006;57(1):133-6.

45. Morris S, Hogan T, McGuire A. The cost-effectiveness of Clozapine: a survey of the literature. Clinical Drug Investigation. 1998;15(2):137-52. Epub 2008/03/29. PubMed PMID: 18370477.

46. Wheeler A, Humberstone V, Robinson G. Outcomes for Schizophrenia patients with Clozapine treatment: how good does it get? Journal of Psychopharmacology. 2009;23(8):957-65. Epub 2008/07/19. doi: 10.1177/0269881108093588. PubMed PMID: 18635713.

47. Kelly DL, Ben-Yoav H, Stock V, Winkler TE, Payne GF, Chocron SE, et al., Development of a lab-on-a-chip biosensor for Clozapine monitoring. American College of Neuropsychopharmacology (ACNP) Annual Meeting; December 2013; Hollywood, Florida, United States.

48. Stock VM, Love RC, Wehring HJ, Kreyenbuhl J, Vyas G, Richardson CM, et al. Identifying barriers to the use of Clozapine for Schizophrenia. American Psychiatric Association Meeting; May 2013; San Francisco, California, United States.

49. Fernandes R, Wu L-Q, Chen T, Yi H, Rubloff GW, Ghodssi R, et al. Electrochemically induced deposition of a polysaccharide hydrogel onto a patterned surface. Langmuir. 2003;19(10):4058-62. doi: 10.1021/la027052h.

Supplemental Information 1

Lab-on-a-chip sensor manufacturing and optimization

The electrochemical micro-chip is modified from previous work (1). Briefly, an array of 3×3 gold working electrodes is patterned using microfabrication technology (radius of 100 µm for amplification characterization, and 500 µm for biofabrication characterization work). A set of on-chip gold counter and pseudo-reference electrodes are included in each of the 3 rows. Photolithography and wet etching processes are used to fabricate the lab-on-a-chip (LOC). 20 nm of chrome and 180 nm of gold were sputtered on 4 inch diameter silicon wafer insulated by 500 nm of silicon oxide formed using plasma- enhanced chemical vapor deposition (PECVD) instrument. The chrome/gold coated wafers were patterned using photolithography, and diced into chips. A consecutive cleaning step using acetone, methanol, isopropanol, "piranha" solution (25% H_2O_2 /75% H_2SO_4), and deionized (DI) water was done prior to experiments. The polydimethylsiloxane (PDMS) chip with the defined chambers was cut from cured slabs of the material and bonded to the electrochemical micro-chip.

All chemicals were purchased from Sigma-Aldrich. Chitosan solution (1%, pH 5–6) was prepared by dissolving chitosan flakes in dilute HCl as previously described (2). All other chemical solutions were prepared in phosphate buffer (PB; 0.1 M, pH 7). Chitosan deposition and catechol modification steps were optimized. An application of a 1.19 A/m^2 cathodic current density was used to fabricate the chitosan film. Then, the catechol was grafted on the chitosan films by immersion in 5 mM catechol and application of +0.6 V, followed by immersion for 5 minutes in deionized (DI) water to discard unbound catechol (Figures 1b: no chitosan and catechol electrical modification steps & 1c: catechol-modified chitosan). Chitosan deposition and catechol grafting times were varied to characterize the fabrication process. Chitosan film height was determined in a Veeco contact profilometer instrument after drying the hydrogel under nitrogen flow. Analytical solutions contained either 110 µL or 12 mL (for micro- and milli-scales solution volumes respectively) of 25 µM hexaammineruthenium(III) chloride ($Ru(NH_3)_6Cl_3$; HARu) and ferrocenedimethanol as an oxidizing mediator. When milli-

scale volume solution was used (for volumes greater than 200 µL), the micro-chip was dipped in a petri dish for testing.

We studied the chitosan electrodeposition rate on the microelectrodes in the presence of either micro- or milli-liter solution volumes of chitosan to obtain better understanding and control of fabrication parameters. Using profilometry of films to characterize the chitosan film thickness, we determined a linear correlation of film thickness with duration of the electrodeposition fabrication step, 3.0 ± 0.6 nm/s for 110 µL (micro-scale volume) and of 5.0 ± 0.8 nm/s for 12 mL (milli-scale volume) (Figure S1a). The difference between the chitosan electrodeposition rates for milli- and micro-liter solutions is likely due to the additional constraints placed on diffusion by the presence of the PDMS chambers. Different micro- and milli- scale distances between the counter and working electrodes may contribute to the observed variability due to non-uniform uncompensated resistance. An optimized chitosan deposition time of 210 seconds (resulted 750 nm dry chitosan thickness) was chosen for further characterization tests to resemble a film thickness similar to our previous macro-scale work.

The impact of the catechol functionalization time on amplification performance was further investigated with solutions of the model oxidizing mediator ferrocenedimethanol. Figure 1Sb demonstrates a positive relationship between catechol grafting time (0–250 seconds) and the total oxidative charge generated between 0 and +0.7 V of a cyclic voltammogram. The positive relationship is expected due to the additional catechol that is available to donate electrons to the mediator. This relation was observed in a previous macro-scale study of the catechol-modified chitosan system (3), indicating that the same redox film properties were obtained in the micro-scale. However, the increase in standard deviation with grafting time indicates a trade-off between amplification and accuracy of the measurement. This may be due to physical variations in chitosan matrix density at the electrode affected by longer grafting times.

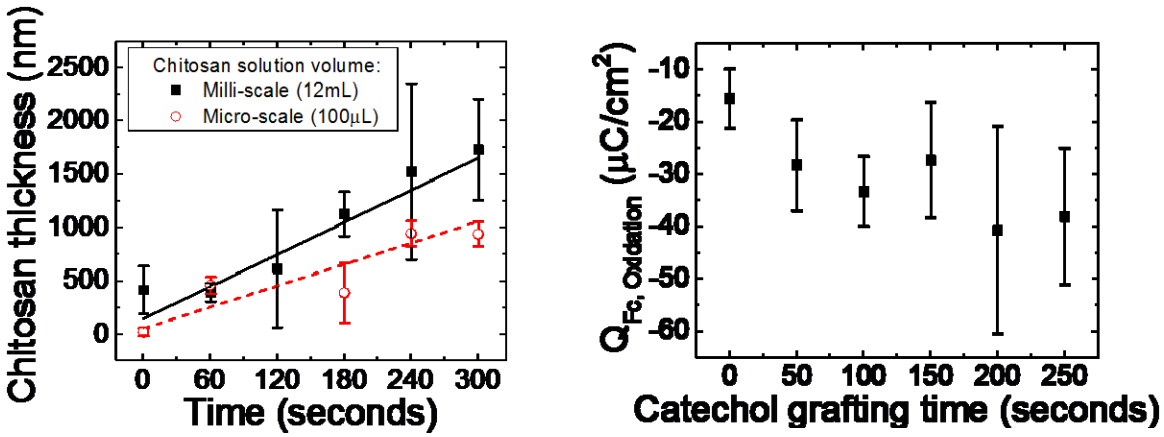

Figure S1. (a) The influence of the electrodeposition duration on the chitosan thickness with milli- and micro-scale solution volumes. (b) The effect of catechol grafting duration on the amplification of ferrocenedimethanol oxidative charge generated between 0 V and +0.7 V of a cyclic voltammogram (210 seconds chitosan deposition, 110 µL solution).

References:

1. Ben-Yoav H, Dykstra PH, Bentley WE, Ghodssi R. A Microfluidic-based electrochemical biochip for label-free diffusion-restricted DNA hybridization analysis. Biosensors and Bioelectronics. 2012;38(1):114-20.

2. Fernandes R, Wu L-Q, Chen T, Yi H, Rubloff GW, Ghodssi R, et al. Electrochemically Induced deposition of a polysaccharide hydrogel onto a patterned surface. Langmuir. 2003;19(10):4058-62. doi: 10.1021/la027052h.

3. Kim E, Liu Y, Shi X-W, Yang X, Bentley WE, Payne GF. Biomimetic approach to confer redox activity to thin chitosan films. Advanced Functional Materials. 2010;20:2683-94. doi: 10.1002/adfm.200902428.

Supplementary Information 2

"Identifying Barriers to the Use of Clozapine for Schizophrenia" survey questions

Identifying Barriers to the Use of Clozapine for Schizophrenia

A. Clozapine Use:

For the following statements bellow, please describe your experience in prescribing clozapine and select the one response that best describes your practice.

1a. Have you ever prescribed clozapine?

1. ☐ Yes
2. ☐ No

***** **STOP** (If not yes then go to question 3, else continue) *****

1b. If yes, for approximately how many patients?

1. ☐ 1-5
2. ☐ 6-10
3. ☐ 11-15
4. ☐ 16-20
5. ☐ 21-25
6. ☐ 26+

2a. Have you prescribed clozapine in the past year?

1. ☐ Yes
2. ☐ No

***** **STOP** (If not yes then go to question 3, else continue) *****

2b. If yes, for approximately how many patients?

1. ☐ 1-5
2. ☐ 6-10
3. ☐ 11-15
4. ☐ 16-20
5. ☐ 21-25
6. ☐ 26+

3. If you have never prescribed clozapine, why not? (please select the most significant answer)

1. ☐ Too much trouble
2. ☐ Not on formulary
3. ☐ Too many side effects
4. ☐ No experience with prescribing
5. ☐ Patients do not qualify for prescription
6. ☐ Not applicable to my practice setting
7. ☐ Other Please specify:

_____

_____

Please complete the questionnaire below even if you have never prescribed clozapine.

Please select one of the following ratings to answer questions 4 to 31.

1= Never or likely not
2= Not likely
3= Sometimes
4= Mostly
5= Always or significantly

B. Non-Clinical Barriers to Use of Clozapine:

For the following statements below, to what extent does the statement limit your more widespread use of clozapine? Please answer in your opinion only.

4. Process of signing-up self to clozapine registry(ies).

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

5. Process of singing-up your patient to clozapine registry(ies).

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

6. Time spent on administrative tasks to get patient started on clozapine.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

7. Lack of structure in your practice setting to facilitate clozapine prescribing and monitoring.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

8. Lack of a centralized comprehensive system where all registry, pharmacy, and laboratory data can be stored and accessed.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

9. Lack of educational and marketing materials.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

10. More aggressive marketing of other antipsychotic medications.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

11. Cost of clozapine.

1 ☐ Never or likely not | 2 ☐ Not likely | 3 ☐ Sometimes | 4 ☐ Mostly | 5 ☐ Always or significantly

C. Clinical Barriers to Use Clozapine:

For the following statements below, to what extent does the statement limit your more widespread use of clozapine? Please answer in your opinion only.

12. Limited experience with clozapine prescribing during residency training.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

13. Not feeling competent prescribing clozapine.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

14. Need for initial titration of clozapine

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

15. Lack of connectivity between inpatient and outpatient treatment settings.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

16. Need for even closer monitoring of patient then with other antipsychotics.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

17. Patients may not be adherent to clozapine treatment.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

18. Burden of mandatory weekly/bi-monthly/monthly blood draws on patient.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

19. Patients may not be adherent with blood work.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

20. Delay/error in WBC collection/report to pharmacy may cause delay/failure to dispense medication to patient.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

21. Benign ethnic neutropenia: patients having a low neutrophil count at baseline.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

22. Little understanding of interpretation of clozapine blood levels.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

D. Side Effects of Clozapine:

For the following statements below, to what extent does the statement limit your more widespread use of clozapine? Please answer in your opinion only.

23. Potential risk for agranulocytosis or neutropenia.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

24. Potential risk for cardiomyopathy.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

25.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

26. Potential risk for metabolic syndrome, including weight gain, increased cholesterol, hypertension, or diabetes mellitus.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

27. Potential risk for extrapyramidal side-effects, including pseudo-parkinsonism, akathisia, dystonia, or tardive dyskinesia.

☐	☐	☐	☐	☐
1	2	3	4	5
Never or likely not	Not likely	Sometimes	Mostly	Always or significantly

28. Potential risk for gastrointestinal hypomotility resulting in constipation or impaction.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	**Not likely**	**Sometimes**	**Mostly**	**Always or significantly**

29. Potential risk for hypersalivation.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	**Not likely**	**Sometimes**	**Mostly**	**Always or significantly**

30. Potential risk for drowsiness.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	**Not likely**	**Sometimes**	**Mostly**	**Always or significantly**

31. Interactions with other medications.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Never or likely not	**Not likely**	**Sometimes**	**Mostly**	**Always or significantly**

32. Other barriers (not mentioned above), please specify _____

_____

_____

Please select one of the following ratings to answer questions 33 to 45.

1= Strongly disagree
2= Somewhat disagree
3= Neutral
4= Agree
5= Strongly agree

E. Possible Solutions for Improving Clozapine Utilization:

How strongly do you believe the following can facilitate the prescribing of clozapine in your practice?

33. More time dedicated to learning about clozapine with emphasis on practical use and solutions to its challenges during residency training.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

34. Comprehensive CME lectures in your facility or dedicated symposiums

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

35. Free internet-based educational programs for prescribers, including section for patients' education.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

36. Centralized internet-based database for physician, patient, and pharmacy clozapine registries, blood work results, and other information regarding patient care.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

37. Simplified blood draws for WBC, ANC and clozapine levels in the form of fingersticks or a specific point-of-care device with clinical staff collecting results in your office.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

38. Simplified blood draws for WBC, ANC and clozapine levels in the form of fingersticks or a specific point-of-care device available at local pharmacy.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

39. Simplified blood draws for WBC, ANC and clozapine levels in the form of fingersticks or a specific point-of-care device available to patient or to caregiver in his/her home with results transmitted directly to your office.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

40. Modified clozapine prescribing guidelines that permit less frequent blood draws.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

41. Modified clozapine prescribing guidelines that permit lower WBC and ANC thresholds in patients with benign ethnic neutropenia.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

F. Improving Clozapine Use with Point of Care Monitoring:

Point of care devices to assist blood monitoring in real time are in various stages of development. Please comment
on how strongly you agree or disagree with the following:

42. A specific test that would provide immediate WBC and ANC results would increase my use of clozapine.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

43. A specific test that would provide immediate clozapine blood levels would increase my use of clozapine.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

**44. An available device that could electronically transmit data from patient home testing for WBC, ANC
and clozapine level blood testing outside the office would increase my use of clozapine.**

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

45. Immediate results by point-of-care device would be an improvement over waiting for blood test results to return from the laboratory.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
Strongly disagree	Somewhat agree	Neutral	Agree	Strongly agree

46. Which of the following point of care types of device you would be interested in using: (select one or more)

a) ☐ patch
b) ☐ handheld
c) ☐ implantable
d) ☐ attached or worn on body
e) ☐ urine test
f) ☐ regular blood draw

47. If you could receive electronic blood test results (ANC, WBC or clozapine levels) whenever you wanted, at what frequency would you find it most useful? (select one)

a) ☐ every month
b) ☐ biweekly
c) ☐ once a week
d) ☐ twice a week
e) ☐ three times a week
f) ☐ once a day
g) ☐ twice a day
h) ☐ four times a day

G. Demographics:

48. Gender: (select one)

1. ☐ Male
2. ☐ Female

49. Age in years: (select one)

1. ☐ 25-35
2. ☐ 36-45
3. ☐ 46-55
4. ☐ 56-65
5. ☐ 65+

50. Ethnicity: (select one)

1. ☐ Hispanic or Latino
2. ☐ Not Hispanic or Latino

51. Race: (select one or more)

1. ☐ American Indian or Alaska Native
2. ☐ Asian
3. ☐ Black or African American
4. ☐ Native Hawaiian or Pacific Islander
5. ☐ White
6. ☐ Other, specify_____
7. ☐ Unreported

52. Professional information (select one):

1. ☐ Psychiatry Resident or Fellow
2. ☐ Boards Eligible or Boards Certified Psychiatrist
3. ☐ Other: specify_____

53. Subspecialty (select one or more):

1. ☐ Adult Psychiatry
2. ☐ Child and Adolescent Psychiatry
3. ☐ Geriatric Psychiatry
4. ☐ Emergency Psychiatry
5. ☐ Consultation Liaison
6. ☐ Forensic Psychiatry
7. ☐ Substance Abuse
8. ☐ Clinical Research
9. ☐ Other: specify_____

54. Work Description/Setting (select one or more):

1. ☐ Does not apply (resident/fellow)
2. ☐ Inpatient or Partial Hospitalization
3. ☐ Psychiatry ER
4. ☐ Consult Liaison
5. ☐ Outpatient Clinic or Private Practice
6. ☐ Community Mental Health Center
7. ☐ Correctional or Forensic Facility
8. ☐ Nursing Home
9. ☐ Residential Treatment Center
10. ☐ Student/College Mental Health
11. ☐ Other, Specify_____

55. Number of years in practice (select one):

1. ☐ Still in residency/fellowship
2. ☐ 1-5
3. ☐ 6-10
4. ☐ 11-15
5. ☐ 16-20
6. ☐ 21-25
7. ☐ 26+

56. What is the approximate percentage of patients diagnosed with a psychotic disorder (ie., schizophrenia, schizoaffective disorder or psychotic disorders NOS) in your practice? (select one)

1. ☐ 0-10%
2. ☐ 11-25%
3. ☐ 26-50%
4. ☐ 50%+

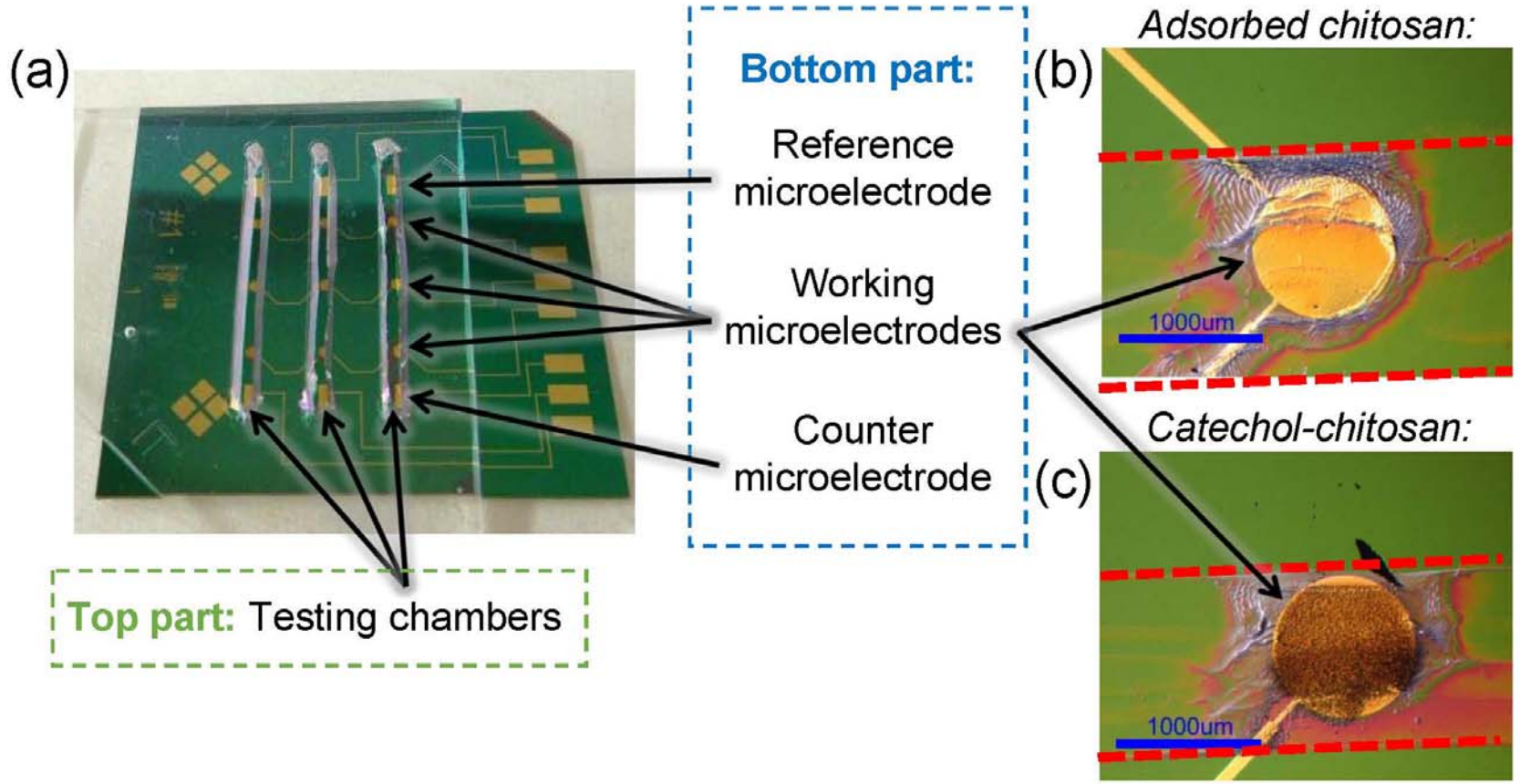

Figure 1. (a) Photograph of the fabricated arrayed electrochemical LOC (3.5 cm × 4 cm), a single microelectrode with (b) no chitosan and catechol modifications (chitosan residues due to chitosan solution in the chambers without electrical current application) and (c) catechol-chitosan modifications (210 seconds chitosan deposition followed by 150 seconds catechol functionalization). Red dashed lines indicate the chamber's boarders.

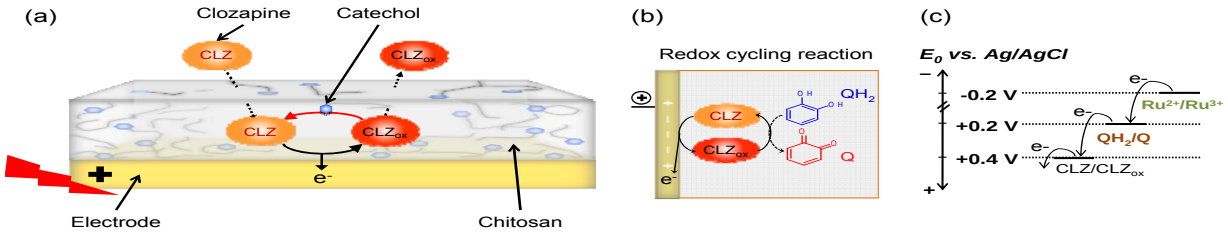

Figure 2. CLZ as an oxidizing mediator in the catechol-chitosan system. (a) Schematic of the CLZ oxidation/reduction cycle for signal amplification. (b) Continuous oxidation of CLZ in the presence of catechol (Q) reduction. (c) CLZ acts as an oxidizing mediator of QH_2, and Ru^{2+} as a reducing mediator regenerating the Q.

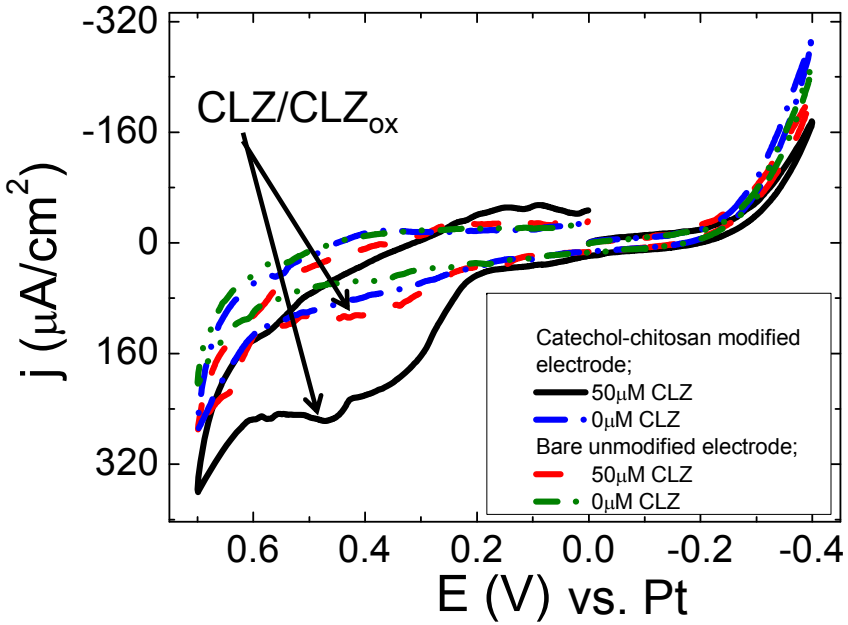

Figure 3. Cyclic voltammograms in the presence and absence of CLZ with either bare unmodified (with CLZ – dashed red; without CLZ – dash-dot-dotted green) or catechol-modified chitosan (with CLZ – solid black, without CLZ – dash-dotted blue) electrodes. Arrows indicate CLZ oxidation peaks.

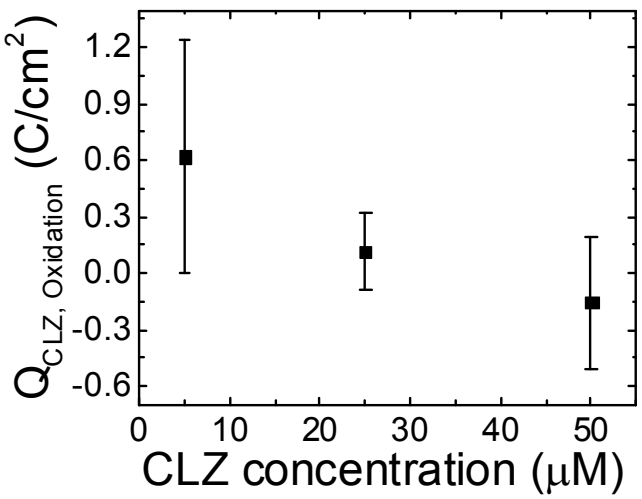

Figure 4. CLZ detection in 110 μL buffer solutions with 5, 25, and 50 μM concentrations. Y-axis values are the total oxidative charge calculated between 0 V and +0.7 V from measured cyclic voltammograms. Optimized biofabrication duration parameters of 210 and 50 seconds for chitosan electrodeposition and catechol grafting, respectively.

Table 1.

Demographic Information of Survey Results (N=255)		
	Categories	Values
Sex	Male	134 (53%)
Age*	25-35 years 36-45 years 46-55 years 56-65 years 65+ years	48 (19%) 49 (19%) 56 22%) 54 (21%) 45 (18%)
Race**	White	185 (73%)
Years in practice	Still in training 1-10 years 11-20 years 20+ years	45 (18%) 44 (18%) 47 (19%) 115 (45%)
Treatment of Psychotic Disorders	>50% of patients	31 (12%)
Clozapine Prescribing	Ever Last Year	217 (85%) 131 (61%)

*3 missing race
**4 missing years in practice
Table 1. Survey results. Demographic information (277/860; 32% responded).

Table 2.

Results Reported from Survey	Questions on Survey		Mean Value and SD from Likert scale*
Ten Top Ranking Barriers (Among 28)	Patients likely nonadherent to blood work		3.7 ± 1.1
	Burden of blood draws on patient		3.6 ± 1.2
	More monitoring than other antipsychotics		3.2 ± 1.2
	Medication nonadherence		3.2 ± 1.1
	Risk of neutropenia		3.0 ± 1.0
	Risk or weight gain and associated complications		3.0 ± 1.0
	Delay in WBC may delay medication		2.8 ± 1.2
	Lack of structure to facilitate prescribing		2.8 ± 1.4
	Time spent administratively to start		2.7 ± 1.2
	Inpatient to outpatient disconnection		2.7 ± 1.2
Five Top Ranked Solutions (Among 9)	WBC and CLZ levels in office		4.0 ± 1.1
	WBC and CLZ levels at pharmacy		4.0 ± 1.0
	Centralized internet based database for registration, results and other information		3.9 ± 1.1
	WBC and CLZ levels at home		3.8 ± 1.2
	Modified CLZ prescribing guidelines permitting less frequent blood draws		3.8 ± 1.1
Device Feasibility	POC device would improve care		3.9 ± 1.0
	POC device with WBC would increase CLZ use		3.6 ± 1.1
	POC device with CLZ levels would increase CLZ use		3.3 ± 1.0
	Immediate transmitted results would increase use of CLZ		3.5 ± 1.0
	Type of device highest ranked		59% handheld
Interested in Using Handheld Monitoring Device	Females vs. males	65% vs. 53%	p=0.052
	Residents vs. board certified	73% vs. 55%	p=0.02
	Prescribers of CLZ vs. never prescribed	61% vs 45%	P=0.056

*Mean and SD of the Likert Scale score reported. Results are listed in descending order with most agreement to statement listed at the top. This survey asked a series of questions on a 5 point Likert Scale (1 = strongly disagree, 5 = strongly agree) regarding the barriers related to CLZ use, blood draw issues with CLZ, and the physician's interest and willingness to use novel technology and point of care devices to monitor CLZ. In addition, the survey solicited the physician's willingness to increase the utilization of CLZ if LOC technology was available. Mean values above 3 indicate agreement with the statement as 3 was neutral.

Table 2. Survey results. Barriers and device feasibility (277/860; 32% responded).