Evaluation and Applications of the Clinical Global Impressions Scale as a Tool for Measurement-based Care within the Context of a First Episode Psychosis Program

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Abstract

Background: Unlike most areas of medicine, treatment outcomes (response and side effects) are not routinely monitored and adjusted using objective measures (e.g. laboratory examinations, blood pressure, etc.) in psychiatry. Instead, pharmacotherapy for psychiatric disorders is largely based on clinician's expert judgment aided with treatment guidelines. Two concepts, *treatment response* and *resistance,* are often used in these guidelines, however, their definitions are variable and complex. Consequently, there is considerable variability in treatment decisions and quality of care. This variability is especially dire for individuals with first episode psychosis (FEP) where early treatment response may significantly affect the prognosis and quality of life. Many studies have demonstrated that measurement-based care (MBC), the use of systematically collected psychometric assessments, can provide a means of standardization and mend this gap in psychiatric practice. Nevertheless, in clinical practice, MBC is far from routine, especially for psychotic disorders due to a number of organizational, clinician-, and patient-related barriers to implementation.

Objective: This thesis aims to address barriers to MBC implementation in terms of measurement selection, evaluation, and integration at a FEP program. These factors will be addressed in two papers. The first focuses on pragmatic considerations for implementation of MBC in the context of FEP as well as the justified selection and evaluation of the Clinical Global Impressions Scale (CGI). The second paper will focus on illustrating how MBC, using the CGI, could help derive indices of quality of care at the patient and the service levels. Importantly, we propose novel concepts that allow flagging patients that may need therapeutic changes such as the prescription of clozapine, for treatment-resistance.

Methods: In the first study, the CGI was evaluated on feasibility of use in practice, inter-rater reliability, and concurrent validity with well-established research scales. In the second study, CGI ratings were used 1) at the patient level, in the development of an algorithm that may help clinicians to identify patients in need of increased clinical attention and 2) to derive indices of care at the service level. At the patient level, CGI criteria were used to define and operationalize special

clinical situations, namely patients requiring clinical attention (PRCA) and potential resistance to antipsychotic medications. At the service level, aggregate ratings were used to evaluate quality of care in terms of patient improvement and adherence to FEP prescription guidelines.

Results: The first study revealed a good fidelity to practice as well as high interrater reliability of CGI-S ratings between psychiatrists and good concurrent validity of ratings with more sophisticated scales. In the second study, the algorithm detected 19 patients as PRCA of whom the majority (63%) received timely intervention. However, 15 PRCA still met criteria for potential treatment resistance most of whom (53%) were not offered clozapine. At the service level, patients were shown to improve within the first few months of treatment while taking low-doses of antipsychotics, suggesting that the program is adhering to basic FEP treatment guidelines.

Conclusion: This thesis provides evidence in support of using the CGI to provide MBC for individuals with first episode psychosis. The CGI is feasible for clinical routine and captures different dimensions of psychosis. Furthermore, when used to define particular clinical situations, a CGI-based algorithm may serve as a useful accessory for pharmacotherapy decisions. Finally, aggregate CGI data can be used to define quality of care indices that can serve to evaluate services. As such, the CGI along with the algorithm we developed could help significantly advance MBC implementation efforts in psychiatry.

Résumé

Contexte : Contrairement à la plupart des domaines de la médecine, les résultats des traitements ne sont pas systématiquement surveillés et ajustés à l'aide de mesures objectives (ex : examens de laboratoire) en psychiatrie. La pharmacothérapie des troubles psychiatriques est plutôt basée sur le jugement expert du clinicien, aidé par des directives de traitement. Deux concepts, *la réponse* et *la résistance* au traitement, sont souvent utilisés dans ces directives, mais leurs définitions sont variables et complexes. Par conséquent, il existe une variabilité considérable dans les décisions de traitement et la qualité des soins. Cette variabilité est particulièrement importante pour les personnes souffrant d'un premier épisode de psychose (PEP), pour lesquelles une réponse précoce au traitement peut affecter de manière significative le pronostic et la qualité de vie. De nombreuses études ont démontré que les soins basés sur la mesure (SBM), l'utilisation d'évaluations psychométriques recueillies de manière systématique, peuvent combler cette lacune dans la pratique psychiatrique. Néanmoins, dans la pratique clinique, les SBM sont loin d'être une routine, en particulier pour les troubles psychotiques, en raison d'un certain nombre d'obstacles liés à l'organisation, aux cliniciens et aux patients.

Objectif : Cette thèse vise à aborder les obstacles à la mise en œuvre de la SBM en termes de sélection, d'évaluation et d'intégration des mesures dans un programme PEP. Ces facteurs seront abordés dans deux articles. Le premier se concentre sur les considérations pragmatiques pour la mise en œuvre de la SBM dans le contexte du PEP ainsi que sur la sélection et l'évaluation de l'échelle d'impressions cliniques globales (ICG). Le second article se concentre sur l'illustration de la façon dont les SBM, en utilisant l'échelle ICG, pourrait aider à dériver des indices de qualité des soins au niveau du patient et du service. Notamment, nous proposons de nouveaux concepts qui permettent de signaler les patients qui pourraient avoir besoin de changements thérapeutiques, comme la prescription de clozapine, en cas de résistance au traitement.

Méthodes : Dans la première étude, le ICG a été évalué sur la faisabilité de son utilisation dans la pratique, la fiabilité inter-juges et la validité concurrente avec des échelles de recherche bien établies. Dans la deuxième étude, les évaluations de l'ICG ont été utilisées 1) au niveau du

patient, dans le développement d'un algorithme qui pourrait aider les cliniciens à identifier les patients nécessitant une attention clinique accrue et 2) pour dériver des indices de soins au niveau du service. Au niveau du patient, les critères ICG ont été utilisés pour définir des situations cliniques, notamment les patients nécessitant une attention clinique (PNAC) et la résistance potentielle aux médicaments antipsychotiques. Au niveau du service, l'ICG été utilisé pour évaluer la qualité des soins.

Résultats : La première étude a révélé une bonne fidélité à la pratique ainsi qu'une fiabilité inter-juge élevée des évaluations ICG-S entre psychiatres et une bonne validité concurrente des évaluations avec des échelles plus complexes. Dans la deuxième étude, l'algorithme a détecté 19 patients comme PNAC, dont la majorité (63 %) a bénéficié d'une intervention rapide. Cependant, 15 PNAC répondaient encore aux critères de résistance potentielle au traitement et la plupart d'entre eux (53 %) n'ont pas reçu de clozapine. Au niveau du service, l'état des patients s'est amélioré au cours des premiers mois de traitement alors qu'ils prenaient de faibles doses d'antipsychotiques, ce qui suggère que le programme adhère aux directives de base du traitement PEP.

Conclusion : Les échelles ICG sont réalisablent en routine clinique et reflètent les différentes dimensions de la psychose. De plus, lorsqu'elles sont utilisées pour définir des situations cliniques particulières, un algorithme basé sur les ICG peut servir d'accessoire utile pour les décisions de pharmacothérapie. Enfin, les données CGI agrégées peuvent être utilisées pour définir des indices de qualité des soins qui peuvent servir à évaluer les services. En tant que tel, les ICG ainsi que l'algorithme que nous avons développé pourraient contribuer à faire progresser de manière significative les efforts de mise en œuvre du SBM en psychiatrie.

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Contribution of Authors

As first author of this thesis, I (**Michelle Khau**) made a significant contribution to the conceptualization, design, data analysis, interpretation of results, and writing of this thesis. In addition, there are a number of individuals who contributed significantly to this thesis.

Sherezad Abadi, contributed significantly to the CGI integration at PEPP by hosting multiple information sessions for clinicians and clinical staff. She also organized and collected the data of all clinician interrater reliability sessions used in Chapter 3.

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Dr. Karim Tabbane (thesis committee member) contributed significantly to the design and interpretation of results and revisions of Chapter 3 as well as revisions of Chapter 4.

Dr. Patricia Boksa (co-supervisor) contributed significantly to the conceptualization, design, interpretation of results, and revisions of this thesis as a whole.

Dr. Ridha Joober (primary supervisor) contributed significantly to the conceptualization, design, interpretation of results, and revisions of this thesis as a whole. He also contributed significantly to the engagement of relevant stakeholders (clinicians, clinical and research staff, program coordinators) that was necessary for the implementation of the CGI at PEPP.

Chapter 1: Introduction

In medicine, instruments of measurement are important accessories to care. From stethoscopes to blood tests, measurements are used to confirm diagnoses and provide standards for ongoing monitoring of symptoms and side effects. While there are yet to be objective biological assessments for symptoms and side effects in psychiatry, psychometric scales were developed to perform a similar function. The systematic use of these psychometric measures to inform treatment decisions is widely referred to in the literature as measurement-based care (MBC). Many clinical studies have demonstrated evidence for the superiority of MBC over regular psychiatric care alone in terms of treatment outcomes and patient satisfaction (Scott & Lewis, 2015; Fortney et al., 2017; Aboraya et al., 2018). Presently, MBC is routinely used in research such as clinical trials. However, the majority of clinicians do not incorporate any form of MBC in their routine practice (Fortney et al., 2017). Ultimately, adherence to prescription guidelines vary and this methodological dissonance between research and practice may negatively impact patient outcomes (Institute of Medicine (US) Committee on Quality of Health Care in America, 2001; Hatfield et al., 2010).

In addition to illness management, systematic measures provide a standard basis on which to evaluate quality of care, align financial incentives with patient needs, and inform continuous improvement of care and services. Similarly, MBC can potentially act as this "interlocking infrastructure" that is currently missing in psychiatry (Harding et al., 2011).

Given these benefits, significant research efforts have been dedicated to identifying barriers to MBC implementation and possible solutions (Garland et al., 2003; Hatfield & Ogles, 2007; Fortney et al., 2017; Lewis et al., 2019). A frequently-proposed solution is the implementation of MBC using patient-rated scales. This solution has demonstrated significant success within the context of affective disorders demonstrating increased patient satisfaction with care as well as superior treatment outcomes compared to treatment without patient-rated input (Trivedi et al., 2006; Guo et al., 2015; Scott & Lewis., 2015; Fortney et al., 2017; Lewis et al., 2019). However, the question of insight has long been a concern for the validity of patient-rated measures in the context of psychotic disorders. A review by Bell et al. (2005) examining the validity and use of patient-rated measures in context of psychotic disorders revealed evidence for the validity of self-report measures on quality of life as well as personality, temperament, and interpersonal problems,

while the validity of self-reports on symptoms (positive, negative, depressive, and functioning) tended to vary. Additionally, one study found that individuals with first episode psychosis demonstrated less symptom awareness than multiple episode patients diagnosed with schizophrenia (Thompson et al., 2001). It seems that individuals with psychotic disorders, especially those with first episode psychosis, lack the necessary level of symptom insight required for the validity of self-assessment measures within the context of MBC (Thompson et al., 2001; Keshavan et al., 2004). As such, an important question remains, how can MBC be implemented in psychiatric practice for the care of individuals with psychotic disorders? This question must first be dissected in terms of the present context of care and MBC solutions that have only recently been proposed.

Chapter 2: Literature Review

2.1 Pharmacological Treatment monitoring in Psychiatry: Present Context and Limitations

The aim of treatment in the majority of chronic disorders is the control and resolution of symptoms. When using pharmacological treatments, symptoms must be managed while minimizing side effects. Thus, treatment decisions are often based on a combination of clinical judgment and standardized testing (i.e., blood tests), however, such biological testing is not yet possible in psychiatry. Instead, assessment and decisions in the course of pharmacotherapy of psychiatric disorders are largely based on clinician's expert judgment aided with treatment guidelines that outline best practices and intervention strategies. These guidelines are only useful if the clinician can systematically track changes of the clinical condition of the patient (improvement and deterioration) over time. Another important condition to improve this process is the reliance on guidelines that specify clearly what exactly constitutes a response, or lack thereof, to treatment.

For instance, treatment resistance in schizophrenia is described by the World Federation of Societies of Biological Psychiatry (WFSBP, 2012) as "non response to treatment at recommended dosage for a duration of at least 6-8 weeks with at least 2 antipsychotics, one of which should be an atypical antipsychotic (Hasan et al., 2012)." Since there is no description of criteria for non-response in terms of residual symptom severity or side effects, this is left to interpretation. This might represent also a practical challenge to clinicians who need to make treatment decisions based on each patient's unique history of symptom fluctuations and medications. Additionally, this can

be overwhelming and a number of studies reviewing the accuracy of therapist judgment alone have found that it is prone to inaccuracies in terms of detecting client deterioration, and is often worse at detecting no change in client progress (Hatfield et al., 2010; Hannan et al., 2005). Consequently, there are discrepancies in clinician adherence to certain prescription guidelines. Overall, the current method of monitoring treatment progress in psychiatry is not ideal. Improvements in both the monitoring of symptoms and subsequent clinician decision-making is needed.

2.2 Measurement Based Care (MBC)

Measurement Based Care (MBC) is a term coined by Trivedi et al. (2006) and defined as "the routine measurement of symptoms and side effects at each treatment visit and the use of [this data] to modify medication doses." Critical decision points are predefined as one or many rating cut-off(s) on a selected measure such that once patient assessments meet these criteria, the clinician is prompted to evaluate the clinical situation and intervene if necessary. While the term MBC may be recent in psychiatric literature, the practice of basing care on standardized symptom assessments has been routine in clinical research for decades. In particular, the development of ratings scales and the publishing and widespread use of the Diagnostic and Statistical Manual, Third Edition (DSM-III) in the second half of the 20th century were important catalysts to MBC (Aboraya et al., 2018). These developments were intertwined with the development of clinical trials to assess the efficacy and safety of new psychotropic medications for all major psychiatric disorders (Donlon et al., 1980; Garfinkel, 1980; Fabre, 1992; Bollini et al., 1999; Wachtel et al., 2002). Since most of these trials used standardised scales as measures of efficacy and effectiveness, many treatment guidelines reflected this methodology. Notably, one of the earliest clinical practice guidelines for the treatment of depression in primary care, recommended the regular measurement of symptoms to optimize dosage and personalize treatment for each patient (Agency for Healthcare Policy and Research, 1993). While such guidelines were published, pharmacotherapy algorithms detailing prescription practices were also being developed for many of the major psychiatric disorders (Calabrese & Woyshville, 1995; Zerate et al., 1995; Amsterdam & Hornig-Rohan, 1996). As such, the Texas Medication Algorithm project (TMAP; Rush et al., 1999) sought to align this accumulation of clinical knowledge with the first large-scale initiative at MBC implementation in an outpatient setting. The project aimed to derive consistent pharmaceutical-based treatment practices for individuals with schizophrenia, bipolar disorder, as well as major depressive disorder

(Rush et al., 1999). While the goal was to derive best prescription practices, the TMAP approach to care using MBC procedures in combination with medication algorithms proved more effective than treatment as usual (Adli et al., 2006).

This MBC algorithmic approach to pharmacological treatment has since been referred to in the literature as measurement feedback systems, evidence-based assessment, …etc. Regardless of terms used, the two central components are: 1) systematic treatment tracking and 2) subsequently optimized treatment decisions (Hunsley & Mash, 2007; Bickman, 2008; Harding et al., 2011; Waldrop & McGuinness, 2017; Scott & Lewis, 2015). The TMAP effectively set the foundation for what is defined as MBC today in pharmacological treatment and the patient-level benefits have since been replicated and extrapolated beyond, to benefits at the service and organizational levels as well.

2.2.1 Primary Benefits of MBC: Treatment Optimization & Patient-Centered Care

The primary benefits of MBC are patient-oriented, in terms of treatment outcomes and perceived quality of care. MBC takes an incremental approach to care wherein treatment decisions are constantly informed by the patient's unique needs at the time of assessment. Thus, clinicians can deliver highly personalized treatment and ensure timely intervention for the best possible outcomes for the patient. Especially, when patient-rated measures are incorporated, MBC has been shown to increase patient-satisfaction of care and enhance the therapeutic relationship between patients and service providers (Bauer et al., 2006; Scott & Lewis, 2015; Fortney et al., 2017; Aboraya et al., 2018). Additionally, the systematic nature of MBC allows timely identification of instances that necessitate medication adjustment. These elements have contributed to significantly improved therapeutic outcomes such as increased remission rate and decreased time to remission (Guo et al., 2015; Trivedi et al., 2006; Scott & Lewis., 2015; Lewis et al., 2019). In the literature, MBC has consistently been shown to yield superior results to usual care alone. A meta-analysis by Lambert et al. (2003) reviewed comparison studies of usual psychiatric care *vs* MBC where clinicians were alerted whenever clients were "not on track" according to individual ratings on the Outcome Questionnaire-45 (OQ-45; Lambert, et al., 1996). The sample treated with MBC not only showed lower rates of deterioration but demonstrated a more cost-effective model of care since time was more efficiently managed. The detection of individuals who were not on track led to more

treatment sessions while those who were constantly on track received less treatment sessions. As such, in addition to improving individual patient outcomes, there are a number of secondary benefits to MBC.

2.2.2 Secondary Benefits of MBC: Clinical Practices and Service Planning

Once MBC is systematically used and collected within an organization, aggregated data may inform internal performance evaluations and improvement strategies. For instance, this data can serve as feedback for clinicians at the individual level and has been demonstrated to promote adherence to clinical treatment guidelines (Goebel, 1997; Trivedi & Daly, 2007). At the organizational level, aggregate data would allow rigorous monitoring of interventions and new clinical programs to inform overall quality of care improvement efforts (Scott & Lewis, 2015; Fortney et al., 2017). Finally, this data can also be used to optimize service planning in terms of resources and funding allocation (Lewis et al., 2019; Connors et al., 2021). Thus, in addition to improving individual patient outcomes, MBC data can be aggregated and serve as a general strategy of evaluation to optimize medical services at the organizational level.

2.3 MBC Implementation: General barriers

Despite these benefits, the majority of mental health providers do not engage in any form of MBC in clinical practice (Hatfield & Ogles, 2007; Fortney et al., 2017). Moreover, when providers do engage in MBC, benefits demonstrated from research are not reproduced as MBC is rarely applied according to its empirically informed schedule of every clinical encounter. In fact, as little as 5% of mental health professionals report using measures every 1-2 sessions while almost 50% indicated they would rather never have to administer these measures (Jensen-Doss et al., 2018). Nevertheless, the benefits of MBC are undeniable and the call for implementation is currently echoed across psychiatric disciplines (Fortney et al., 2017; Connors et al., 2021; Dinakaran et al., 2020).

As such, there has been increasing efforts to identify and overcome implementation barriers in psychiatric practice. These barriers were thoroughly explored in a review by Lewis et al. (2019) where they identified 3 broad categories of impediment: individual (patient & practitioner),

organizational, & system-related barriers. For the purpose of this thesis, we will focus on individual and organizational barriers.

Lewis et al. (2019) identified individual, patient-related barriers as confidentiality concerns, response burden (especially if MBC benefits are not easily perceived or integrated into treatment as a form of shared decision-making), and symptom and/or disability interferences for patient-rated scales. Individual, practitioner-related barriers include negative attitudes regarding clinical utility of measurements, lack of time, and lack of incentives. Finally, organizational barriers generally include lack of resources (i.e., training, data collection, and management), especially within smaller clinics where health record data may not be digitalized. A major step towards overcoming these barriers is measurement selection.

2.3.1 MBC in the context of psychotic disorders

The heterogeneous manifestation of symptoms and highly variable treatment responses make individuals with psychotic disorders among the most complex to treat (Case et al., 2011; Clark et al., 2011; Stroup et al., 2018). In addition, individuals with first-episode psychosis have been shown to be particularly sensitive to extrapyramidal side effects (Hasan et al., 2012). In 2005, International clinical practice guidelines and a consensus statement was published with recommendations for the prescription of low-dose antipsychotics when required, followed by careful monitoring of symptoms and side effects (International Early Psychosis Association Writing Group, 2005). However, there are no standards by which adherence to these guidelines are monitored and evaluated. MBC may optimize treatment by allowing a more personal approach to care and help implementing the prescription of lowest effective dose of antipsychotic medications. This is notable within the context of first episode psychosis as quality of treatment, especially during the first 2 to 5 years following a first episode, have been shown to lead to better prognosis and future psychosocial functioning (Birchwood & Jackson, 1998; Malla et al., 2005; Iyer et al., 2015).

In recent meta-analyses examining MBC implementation efforts in psychiatric practice, not a single study included was for psychotic disorders (Fortney et al., 2017; Waldrop, 2017). This is due, in part, to the need for a clinician-rated tool and associated clinician-level barriers. Aboraya

et al. (2018) recently proposed eight criteria to consider whilst selecting a measure, in order to encourage clinician use of MBC in routine practice. The selected measure(s) should be 1) efficient, 2) established as reliable and valid, 3) user-friendly and a reflection of what clinicians do in clinical settings, 4) brief and simple, 5) clinically meaningful and useful, covering the criteria and symptom domains of the disorder, 6) clinically relevant to decision-making, 7) easily extractable and not embedded in progress notes, and 8) sensitive to changes induced by medications or psychotherapy.

Additionally, the complexity of psychotic disorders necessitates a high level of symptom insight for accurate use and reporting on assessments. Symptom insight from a patient's perspective has also been referred to as patients' awareness of their illness and has been shown to be particularly impaired for individuals with early schizophrenia and first episode psychosis (Thompson et al., 2001; Keshavan et al., 2004). Given these constraints, and the limited personnel and training resources in routine psychiatric settings, the selected measure should ideally be clinician-rated. However, the multi-dimensional nature of psychotic disorders often requires the use of lengthy or multiple psychometric scales for different illness domains (i.e., psychopathology, cognition, social functioning) (Dinakaran et al., 2020). Both options are not feasible for the time-limited routines of clinicians in regular clinical practice. To accommodate this need, well-established, multidimensional scales, such as the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) have been shortened. Nevertheless, while the PANSS was shortened from 30 to 6 items, it still requires roughly 15 minutes to assess, using its accompanying interview guide (Kølbæk et al., 2018).

2.3.2 The Clinical Global Impressions Scale

The Clinical Global Impressions Scale (CGI; Guy 1976) is a clinician-rated scale that takes into consideration the global and multidimensional state of illness. Once a clinician has examined the patients, the CGI takes less than a minute to complete as it is composed of two, single-item subscales: a measure of global symptom severity at the time of evaluation (CGI-S) and a measure of global improvement (CGI-I). The CGI scoring is considered to be intuitive for clinicians as the scoring is based on a Likert scale of 1-7 with intuitive anchor points (Nierenberg & De Cecco, 2001; Leucht et al., 2005b; Busner & Targum, 2007). For this reason, the CGI has been the focus of a number of linkage studies by Leucht et al. (2005a, 2005b, 2006) in order to derive clinical

relevance for two of the most widely reported assessments in psychotic disorder research: the PANSS and the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986). For example, it has been established that a 15 points improvement on the PANSS is roughly equivalent to a 1-point improvement on the CGI-S, which is now accepted as the definition of the clinical significance for the PANSS (as opposed to statistical significance). Additionally, the CGI is a well-validated tool with an extensive history as a treatment outcome measure in antipsychotic efficacy studies for schizophrenia (Jeste et al., 1997; Kinon et al., 2000; Perry et al., 2001; Merlo et al., 2002; Meltzer et al., 2011; Higuchi et al., 2019) and more recently, in a number of first episode psychosis studies as well (Cotton et al., 2007; Westman et al., 2019; Cavalcante et al., 2020). Taken together, the CGI meets the criteria proposed by Aboraya et al. (2018) and could be a suitable measure on which to base MBC in the care of individuals with psychotic disorders.

2.4 Objectives

The present research aimed to investigate and outline an initial MBC implementation strategy within the clinical context of a FEP program. The objectives of this strategy were two-fold:

1) Evaluation of the suitability of the Clinical Global Impressions Scale, specifically the CGI-Severity subscale, in terms of validity, reliability, and feasibility for routine clinician use in FEP care, and
2) Development and evaluation of a strategy to meaningfully integrate the CGI as part of an MBC approach that would allow quality of care evaluation and optimization at the patient and service levels.

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Chapter 3: Manuscript 1

Title: Pragmatic implementation of the Clinical Global Impression Scale of-Severity as a tool for measurement-based care in a first-episode psychosis program.

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Abstract

Introduction:

Measurement-based care (MBC) is an evidence-based practice wherein clinical decisions are informed by patient data collected throughout treatment. MBC has yielded superior patient outcomes compared to standard care. However, the implementation of MBC in the day-to-day practice, particularly in psychotic disorders, poses several challenges. This study evaluates the clinician-rated Clinical Global Impressions Scale of Severity (CGI-S), for MBC implementation at a first-episode psychosis program.

Methods:

The CGI-S was evaluated in the context of routine care on fidelity to practice, inter-rater reliability among psychiatrists and concurrent validity with scales measuring different domains of psychopathology (SAPS, SANS, GAF, BPRS, PANSS-6).

Results:

A high fidelity to practice (67%) and inter-rater reliability was found (r_{wg} = 0.92). CGI-S correlations were significant and strongest with BPRS (r = 0.55; $p < 0.01$), GAF (r = 0.53; $p < 0.01$), SAPS (r = 0.52, $p < 0.01$), and PANSS-6 (r = 0.41; $p < 0.05$) scores. However, correlations with SANS and PANSS-6 Negative sub-scale were weak.

Conclusion:

Findings suggest the CGI may be used to overcome important barriers towards MBC implementation within the context of first episode psychosis. However, as suggested by data, further improvements in capturing negative symptoms by rating clinicians are needed.

Keywords: measurement-based care, first-episode psychosis, clinical global impressions scale

1. Introduction

Measurement-based care (MBC) can be defined as "the practice of basing clinical care on client data collected throughout treatment" (Scott & Lewis, 2015). This practice of systematic measurement and monitoring is a staple in many areas medicine and plays an essential role in clinical decisions when planning optimal treatment for patients. In psychiatry, rather than physical or laboratory tests, MBC relies on psychometric assessment scales that may be rated by the patients themselves and/or by clinicians or other trained health care professionals. To take a simple example, the regular use of a measure of a patient's severity of illness and ongoing response to treatment could serve to monitor patient progress and verify adherence to treatment algorithms, or to flag non-adherence to recommended best practices (Scott & Lewis, 2015).

In psychiatry, there is also a breadth of literature that suggests MBC results in better patient outcomes (e.g., increased remission rate, improved detection of treatment inertia, and higher rate of treatment response) compared with standard care alone (Trivedi et al., 2006; Guo et al., 2015; Scott & Lewis., 2015; Fortney et al., 2018; Lewis et al., 2019). Notably, most of this evidence has been accumulated within the context of affective disorders – namely depression – and there is a dearth of research looking at MBC in the context of individuals with psychotic disorders.

In recent meta-analyses examining MBC implementation efforts in psychiatric practice, not a single study included psychotic disorders (Fortney et al., 2018; Waldrop, 2017). This disparity is due in part to the complexities associated with psychotic disorders including lack of symptom insight that may necessitate the use of clinician-rated measures in place of patient-rated ones. While a number of short, valid, clinician-rated instruments have been developed in recent years for assessments of schizophrenia and related psychoses, they remain underused (Dinakaran et al., 2020). It has been reported that less than 20% of mental health providers utilize MBC, and only 5% use it according to its suggested schedule (Lewis et al, 2019). The factors that impede the implementation of MBC in psychiatry and the possible remedies to these impediments have only been thoroughly investigated recently. A review of the literature of MBC in the context of behavioural health by Lewis et al. (2019) identifies three domains where impediments to implementing MBC can happen: individual (patient or clinician), organizational, and systemic.

Correspondingly, they also identify approaches to strengthening implementation including: the selection of a brief and psychometrically robust measure on which to base MBC, subsequent monitoring and reporting of the fidelity of implementation, and finally, the development of a clinical algorithm for MBC in practice. The combination of these recommended approaches and the availability of shorter, clinician-rated assessments offer a unique opportunity for us to address the implementation of MBC for individuals with psychotic disorders. To our knowledge, no previous study has yet to apply this knowledge towards an implementation strategy for MBC in the context of treatment for individuals with first episode psychosis.

The purpose of the present study is to describe a general framework and evaluate basic implementation needs of a simple and scalable form of MBC in a first-episode psychosis program. Specifically, we report here on how implementation of MBC was approached, focusing on: (1) the engagement of the different stakeholders in this process, (2) the selection of an appropriate scale (Clinical Global Impressions Scale for Severity; CGI-S), and (3) the assessment of its intake in day-to-day practice, including its reliability and validity when it is assessed by psychiatrists in the context of routine clinical encounters with patients.

2. Methods

2.1 Setting

The general setting in which this implementation initiative was studied is the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal). PEPP-Montreal is a community-focused, clinical academic program aiming to provide comprehensive medical and psychosocial treatment to young individuals experiencing their first episode of psychosis (FEP). Upon entry, patients are offered a choice to provide written informed consent for research participation and only those who have done so are included in this study. The research protocol has been approved by the Ethics Committee of the Douglas Hospital. All participants were outpatients and, as per PEPP-Montreal acceptance criteria, were between 14 and 35 years of age, diagnosed with either affective or non-affective psychosis and who had not received antipsychotic medication for greater than thirty days total in their lifetime.

2.2 Implementation Strategy

Organizational barriers identified by Lewis et al. (2019) include the lack of leadership support, insufficient organizational readiness, and an overall absence of workplace culture that highlights the clinical significance of MBC. As such, we decided that the implementation of MBC be centred on increasing the buy-in of MBC within the PEPP-Montreal with the concrete objective of improving adherence to pharmacological treatment algorithms. The different stakeholders are the clinical and administrative leadership of the program, as well as all the psychiatrists who are taking care of patients at PEPP. A concrete plan for implementation was discussed and agreed with all stakeholders, including:

(1) Selection and schedule of administration of this measure;
(2) MBC will mainly focus on the improvement of pharmacological interventions by facilitating adherence to therapeutic algorithms;
(3) The assessment tool must be administered by psychiatrists as they are the main care providers who advise patients on matters of pharmacotherapy;
(4) One of the major requirements of MBC is systematic measurement at every encounter with the patient to reflect trajectory of symptoms and treatment evolution over time and to optimize implementation of treatment algorithms (Lewis et al., 2020). In line with this recommendation, ratings of a selected MBC scale should be recorded in clinical notes of the patient at each clinical encounter;
(5) The assessment tool must have intuitive ratings, be very simple to administer, and require minimal training before integration into practice;
(6) An acceptable threshold for inter-rater reliability must be achieved for the selected assessment measure;
(7) A good degree of concurrent validity must be achieved for the selected assessment measure.

The last two criteria serve the integrity of measurement procedure, but are also a means to continuously calibrate the selected MBC tool and maintain rating accuracy within the program.

2.3 The Selection of the Clinical Global Impressions Scale (of Severity) for MBC implementation

A review by Dinakaran et al. (2020) summarized routinely used scales in schizophrenia research and their individual feasibility for clinical integration. It is noteworthy that the most common approach to assessment is to use different scales to assess multiple dimensions of schizophrenia (e.g. psychopathology, affective domains, cognitive functioning, etc.). Since most scales require ≥15 minutes to administer, this can be time consuming if added to routine clinical practice. While many scales have been shortened, the majority remain uni-dimensional assessments (Dinakaran et al., 2020).

Additionally, while it is advisable to include some measurements derived from patient-rated scales in MBC, lack of insight is a frequent concern in patients with psychotic disorders including FEP (Thompson et al., 2001; Keshavan et al., 2004). Among the fifteen most routinely used scales in schizophrenia research, none are patient-rated (Dinakaran et al., 2020). As such, self-assessment symptom scales may be difficult to use for the purpose of advising on pharmacological treatment (Thompson et al., 2001; Keshavan et al., 2004). Thus, it is advisable that MBC targeting pharmacological intervention for patients with FEP, relies at least in part, on scales assessed by clinicians.

Following discussion, the Clinical Global Impressions Scale (CGI; Guy 1976) was selected. The CGI is a clinician-rated scale that takes into consideration the global and multidimensional state of illness. It is composed of two, single-item subscales: a measure of global symptom severity at the time of evaluation (CGI-S) and a measure of global improvement since baseline or last evaluation (CGI-I). Both subscales are rated on a scale of 1-7 with intuitive anchor points and provide simple, readily understandable measures of patient severity of illness and progress in routine clinical practice (Nierenberg & De Cecco, 2001; Leucht et al., 2005b; Busner & Targum, 2007). (See Table 1 for anchors with expanded rating guidelines by Busner & Targum (2007)).

Table 1. CGI-S Ratings and Anchor Points*
"Considering your total experience with this particular population, how mentally ill is the patient at this time?"
1 = Normal: *not at all ill, symptoms of disorder not present past seven days* 2 = Borderline mentally ill: *subtle or suspected pathology* 3 = Mildly ill: *clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function* 4 = Moderately ill: *overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication* 5 = Markedly ill: *intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress* 6 = Severely ill: *disruptive pathology, behavior and function are frequently influenced by symptoms, may require assistance from others* 7 = Among the most extremely ill patients: *pathology drastically interferes in many life functions; may be hospitalized*

*Reproduced from Busner, J., & Targum, S. D. (2007). The Clinical Global Impressions Scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont)*, 4(7), 28.

While psychiatrists were asked to rate both the CGI-S as well as the CGI-I in comparisons with the previous assessment, one of the aims in our MBC implementation framework centers on first establishing a good degree of concurrent validation between our selected measure and previously validated scales. Since most routinely used scales in schizophrenia research do not include a rating of improvement, we focused on first evaluating the CGI-S.

2.4 Quality of implementation

Though the CGI-S is a tool with a long history of use in clinical trials and well-established psychometric characteristics, it is essential for an MBC program to ensure this tool retains such characteristics in the clinical context in which it is applied and over time.

2.5 Inter-rater Reliability

One of the major requirements of any measurement is reliability: consistency in usage and comprehension between multiple raters. While there are anchoring points that accompany each

rating on the CGI-S, these anchors are qualitative and therefore vulnerable to a certain degree of subjectivity. As such, it was agreed that inter-rater reliability be measured at each trimestral meeting among the psychiatrists working at PEPP. At each meeting, a psychiatrist volunteered to prepare a case vignette inspired by their practice and to present it in a written format to the group of psychiatrists. Psychiatrists present at the meeting were asked to rate the CGI-S based on this vignette and ratings were anonymously collected. Given that the CGI-S relies on the overall clinical experience of the psychiatrist, no specific training was given to the psychiatrist prior to the rating.

The inter-rater reliability (IRR) was then calculated and provided to the psychiatrists with some discussion regarding ratings that departed significantly from the median rating (equal or more than 2 points departure). Here, we report on a total of 4 IRR sessions held between January 2017 and September 2019 (8-10 clinicians were present at each session).

2.6 Concurrent validity of the CGI-S

Another major requirement of any measurement is validity; that is, whether the proposed scale correctly measures the constructs it is intended to measure. This could be pursued, in part, by demonstrating concurrent validity through strong correlations between the proposed tool and similar, previously validated psychometric tools. The objective simplicity of the CGI-S for clinicians has prompted multiple equipercentile linkage studies to derive CGI-S equivalencies with the aim of facilitating clinician interpretation of the psychometric tools themselves as well as clinical trial results, often reported as rating cut-offs on these tools. Equivalent CGI-S ratings have been derived for some of the most commonly used scales in schizophrenia research including: The Brief Psychiatric Rating Scale (BPRS), the General Assessment of Functioning scale (GAF), the Scale for the Assessment of Negative Symptoms (SANS), and the PANSS (Leucht et al., 2006; Rabinowitz et al., 2010; Levine et al., 2013; Samara et al., 2014). The same studies also demonstrated a high correlation between ratings on these scales and the CGI-S.

In this project, we took advantage of retrospective data on the CGI-S and several rating scales to conduct a “snapshot” concurrent validity of the CGI specifically within our clinical setting. In addition, we reasoned that an ongoing process of dynamic validation and feedback to the clinicians

would be needed to guard from significant drift in ratings and to maintain a dynamic alertness of the CGI-S raters to the validity process.

2.6.1 Snapshot concurrent validity

The term snapshot was chosen to emphasize the static nature of CGI-S ratings used for this portion of concurrent validation. As part of patients' evaluation during the 2 years of treatment at PEPP, systematic case reviews are conducted for each patient at month 12 and 18 at which point the CGI-S rating is discussed by the entire clinical team and noted in the file. As such, the snapshot concurrent validity of the CGI-S was based on these case review CGI-S ratings that capture a clinical picture of the patient that is specific to month 12 and month 18 of treatment. Other measures were routine evaluations conducted on a roughly monthly basis with the following scales: the Scale for the Assessment of Positive Symptoms (SAPS) and SANS (Andreasen, 1982,1983; Andreasen, 1984), which are complementary and mainly assess symptomatology, the BPRS (Lukoff et al., 1986) with 24 items, and the GAF (Endicott et al.,1976). For the purpose of this study, only patients with completed ratings on all relevant psychometric scales (SAPS, SANS, BPRS, and GAF) at their month 12 and/or their month 18 assessments were included. A total of 58 patients admitted to PEPP-Montreal between May 2015 and October 2018, had completed research evaluations (SAPS, SANS, BPRS, & GAF), and had CGI-S assessed at the 12-month (N = 38) and 18-month (N = 37) case reviews and had also accepted to be included in the research program. Out of this sample, only 17 patients had assessments completed for both month 12 and 18 case reviews. Of the 58 patients, 62% were male and 38% were female with an average age of 23 years.

2.6.2 Dynamic concurrent validity

In addition to retrospectively comparing snapshot CGI-S ratings as described in the previous section, we wished to assess a more dynamic concurrent validity other than months 12 and 18 of treatment, such as earlier stages. As such, we chose the term dynamic to emphasize this comparison of CGI-S ratings to ratings taken at various time points along the clinical encounters between the patient and the treating team between month 1 to month 24 of treatment. In this case, the comparison measure was another scale that is valid, short and that captures major aspects of the psychopathology of psychotic disorders: The Positive and Negative Syndrome Scale-6 (PANSS-

6; Østergaard et al., 2016). We decided to select 10 to 20 percent of patients with completed CGI-S ratings during their monthly scheduled evaluations to be invited, immediately after the psychiatric encounter, to a more structured evaluation using the PANSS-6, a measure that was designed to bridge the measurement gap between research and clinical care in schizophrenia; and comprises brief assessments on 3 positive (P1-Delusions, P2-Conceptual disorganization, P3-Hallucinations) and 3 negative (N1-Blunted Affect, N4-Social withdrawal, N6-Lack of spontaneity and flow of conversation) symptoms. The PANSS-6 has been shown to be scalable; suggesting that its total score can be used to reflect the overall severity of the disorder (Østergaard et al., 2016). In addition, a Short Negative and Positive Symptoms Interview has been published with which to rate the PANSS-6 (SNAPSI; Østergaard, 2017). Patients treated between January and November 2019 were approached during their scheduled monthly appointment. However, since these patients were at different stages of treatment, they were pseudorandomly chosen to ensure an even distribution of patient rating data between month 1 to month 24 of treatment at the clinic. The CGI-S was completed by the clinician on the same day and always collected from the patient file after the rating of the PANSS-6 to avoid biases. A total of 25 patients were recruited and assessed on the PANSS-6. The majority of the sample was male (75%) and average age was 23 years old.

2.7 Fidelity to Practice

Since MBC is an evidence-based practice, optimal results hinge on the proper application of our selected measure according to its intended schedule. For this reason, part of our implementation strategy outlined a protocol wherein the CGI should be rated by the clinician at every clinical encounter with every patient. This protocol was monitored for fidelity to practice and such monitoring has been shown to result in better implementation and sustained application of evidence-based practices in psychiatric research and clinical practice (Bond & Drake, 2019). Especially in early stages of implementation, fidelity monitoring may provide insight into deficiencies such as the need for additional motivational factors or resources (Bond et al., 2009). As such, fidelity was monitored to determine the ease in uptake of practice as an indicator of feasibility for the CGI to be integrated into the psychiatrist's routine. The frequency of CGI-S ratings per psychiatrist was collected by a research assistant during two 6-month periods and was evaluated in terms of 1) protocol met per patient (out of all patients for whom the psychiatrist was

responsible) as well as 2) protocol met per visit (out of all clinical visits with every patient for whom the psychiatrist was responsible).

3. Statistical analyses

All statistical tests and analyses (except for the inter-rater reliability) were completed using SPSS Statistics 24.

3.1 Inter-rater reliability

Due to the anonymous nature of rating collection between IRR sessions, rater 1 – 10 represented different psychiatrists between IRR sessions. Additionally, there was low within-rater variance as the largest difference between two raters was 2. For these reasons, the Finn coefficient of IRR (r_{wg}) was computed rather than other measures of IRR. The Finn coefficient was computed for ratings at each of the 4 interrater reliability sessions, using Excel. The overall IRR was reported as the average Finn coefficient across the 4 sessions.

3.2 Concurrent validity

Spearman rank-order correlations were calculated to compare the correlations between the CGI-S and each individual measure (SAPS, SANS, BPRS, GAF, & PANSS-6). Additionally, the PANSS-6 was broken down into its positive symptom (3-items) and negative symptom (3-items) scales and individually compared with the CGI-S. All p-values of 0.05 or less were considered statistically significant.

4. Results

4.1 Fidelity to the practice

Table 2 provides the details of the conformity to protocol during two periods by psychiatrists. The average fidelity to practice for rating the CGI-S at every clinical encounter varied significantly. Depending on the psychiatrist, this value ranged from 0% to 100% per patient and 30% to 91% per visit. However, fidelity was higher for psychiatrists who saw proportionally more patients and overall average conformity to protocol was 66.6% per client and 66.8% per visit.

Table 2. Conformity to protocol for each psychiatrist during 6-month periods 1 and 2

Protocol variables	Psychiatrist A	B	C	D	E	F	G	Average
Number of Patients Seen								
Period 1	26	40	27	11	10	4	3	17.3
Period 2	43	25	45	19	17	7	3	22.7
Protocol met per patient (%)								
Period 1	92.3	76	48.8	100	100	50	0	66.7
Period 2	65.1	77.5	46.7	94.7	76.6	71	33.3	66.4
Number of visits								
Period 1	119	92	155	60	69	9	10	73.4
Period 2	203	211	285	122	110	44	20	142.1
Protocol met per visit (%)								
Period 1	90.7	72.8	71	85	79.8	44	30	67.6
Period 2	72.9	73.4	48.8	84.4	69.1	63.6	50	66

Protocol met per patient: percentage of patients with completed CGI ratings out of the total number of patients seen per period, without consideration of patients with multiple visits.
Protocol met per visit: percentage of visits, including patients with multiple visits, with completed CGI ratings out of total number of visits

4.2 Interrater reliability

Overall, there was good concordance between the CGI-S ratings by psychiatrists at each session. Indeed, the majority of psychiatrists rated within one point from the modal value (see table 3). The Finn coefficient of IRR was also calculated and found to be high across all four sessions (88-95% agreement) and on average, IRR was 92%.

Table 3. Inter-rater reliability of CGI-S across 4 sessions with psychiatrists of the Douglas Psychotic Disorders Program

	Individual Clinician CGI-S Ratings*											
IRR Session	Dr. 1	Dr. 2	Dr. 3	Dr. 4	Dr. 5	Dr. 6	Dr. 7	Dr. 8	Dr. 9	Dr. 10	Average CGI-S	r_{wg}
Session 1	5	4	5	5	4	5	4	5	6	5	4.8	0.91
Session 2	6	6	5	4	5	6	5	6	6		5.44	0.88
Session 2	3	3	3	2	3	3	3	4	3		3.00	0.95
Session 3	5	5	5	5	5	5	4	6			5.00	0.95
Session 4	6	5	6	5	6	6	6	7			5.88	0.91
Across 4 sessions												0.92

IRR = Interrater reliability, r_{wg} = *Finn Coefficient of Interrater Reliability,* CGI-S = Clinical Global Impressions Severity Score

*Ratings were anonymously collected at every session. As such, Dr. 1-10 may be a different psychiatrist at each session

4.3 Concurrent validity of CGI-S

4.3.1 Snapshot concurrent validity

Spearman correlation between CGI-S (assessed during month 12 and/or Month 18 case reviews) and corresponding ratings on the SAPS, SANS, BPRS, & GAF are presented in Table 4. At month 12, all correlations were statistically significant (all *p*-Values < *0.01*) and ranged between 0.50 and 0.59, reflecting a strong correlation between the ratings on the CGI and the various scales used to measure psychopathology. At month 18, correlations were statistically significant between the CGI-S and BPRS, GAF, and SAPS (all *p*-Values < *0.05*) and ranged between 0.34 and 0.46, reflecting a low to moderate correlations. However, at month 18, no significant correlation was observed between the CGI-S and SANS scores.

Table 4. CGI-S correlations with SAPS/SANS/BPRS/GAF (*n* = 56)

	Scales	Correlation	
		r_s	*p* value*
Month 12	CGI-S *Vs.* SAPS	0.56**	0.01
	CGI-S *Vs.* SANS	0.50**	0.01
	CGI-S *Vs.* BPRS	0.59**	0.01
	CGI-S *Vs.* GAF	-0.56**	0.01
Month 18	CGI-S *Vs.* SAPS	0.39*	0.05
	CGI-S *Vs.* SANS	0.13	0.45
	CGI-S *Vs.* BPRS	0.46**	0.01
	CGI-S *Vs.* GAF	-0.34*	0.05

r_s = Spearman rank-order correlation coefficient for correlation between CGI and comparison scales; CGI-S = Clinical Global Impressions Severity rating, SAPS = Scale for the Assessment of Positive Symptoms total score, SANS = Scale for the Assessment of Negative Symptoms total score, BPRS = Brief Psychiatric Rating Scale total score, GAF = Global Assessment of Functioning score

*Correlation is 2-tailed. All but 1 correlation (between CGI and SANS in month 18) was statistically significant

4.3.3 Dynamic concurrent validity

Spearman correlation coefficients were also calculated for the sample recruited and assessed on the PANSS-6 (Table 5). A moderate and positive correlation coefficient of 0.41 ($p < 0.05$) was observed between the CGI-S and PANSS-6 total score. Similarly, a moderate and positive correlation coefficient of 0.43 ($p < 0.05$) was observed between the CGI-S and the PANSS-6 positive subscale. However, the CGI-S and PANSS-6 negative subscale had a correlation coefficient of 0.20 and was not statistically significant.

Table 5. CGI-S correlation with PANSS-6 (*n* = 25)

Comparison	Correlation	
	r_s	*p* value*
CGI-S *Vs.* PANSS-6	0.41	0.05
CGI-S *Vs.* PANSS-6-P	0.42	0.05
CGI-S *Vs.* PANSS-6-N	0.20	0.31

r_s = Spearman rank-order correlation coefficient for correlation between CGI and PANSS-6 total as well as positive and negative symptom components; CGI-S = Clinical Global Impressions Severity rating, PANSS-6 = Positive and Negative Syndrome Scale-6 item version total score, PANSS-6-P = PANSS-6 Positive items only, PANSS-6-N = PANSS-6 Negative items only
*Correlation is 2-tailed. All but 1 correlation (CGI and PANSS-6-N) was statistically significant

5. Discussion

Despite the benefits of MBC, there are a number of barriers to implementation. While solutions have recently been identified (Lewis et al., 2019), they have yet to be applied within the context of psychotic disorders. This study investigated an initial step towards MBC implementation: the selection and evaluation of a measure (CGI-S) on which to base MBC within the clinical setting of a first episode psychosis program. The evaluation yielded four significant findings that each support the CGI-S as an appropriate tool for MBC, including a potential method of continuous calibration to ensure sustained validity of ratings.

First, the degree of fidelity to practice was relatively high and stable. While this varied, the psychiatrists with the lowest levels of conformity to practice were also those who saw proportionally less clients. As such, it can be reasoned that the low fidelity to practice was not the result of the CGI being difficult to use, but simply a natural delay in uptake associated with implementation of novel practices. Overall, this supports the feasibility of integrating the CGI into psychiatrists' clinical routines. Second, CGI ratings seem to provide intuitive clinical significance for psychiatrists as indicated by the consistently high interrater reliability between psychiatrists despite no previous CGI training. Third, while most correlations between the CGI-S and more

sophisticated tools were moderate, weak correlations between the CGI-S and the SANS as well as the PANSS-6 negative items seem to suggest that negative symptoms are not captured as well by the CGI-S compared to positive symptoms and functioning interference. Accordingly, a noteworthy finding in our study is the presence of patients with high CGI-S ratings and very low SANS scores. Upon closer examination, the majority of these patients were found to have GAF scores lower than 50 which indicates "serious symptoms or serious impairment in social, occupational, or school functioning." Once again, CGI-S ratings seem to be significantly influenced by symptoms associated with functioning interference. Additionally, the discordance in CGI-S and SANS ratings reflect previous findings that have demonstrated weak correlations between the CGI-S and negative symptoms (Haro et al., 2003; Rabinowitz et al., 2006).

Finally, we propose the use of the PANSS-6 (assessed by a research staff independently from the psychiatrist) as a means of continuous validation in the practice of MBC in psychosis services. The strong correlation we observed between the total PANSS-6 total score and the CGI-S support this method of continuous calibration, especially once negative symptoms are emphasized and better captured by the CGI-S in future practice. This PANSS-6 comparison approach can be used as a means of continuously monitoring CGI-S rating accuracy wherein rating discrepancies may then be addressed with psychiatrists. This practice may improve adherence to MBC practices, and guard against drift in the measurement over time.

5.1 Limitations

This study has a number of limitations. Firstly, the sample sizes were relatively small, in particular, the collection of the PANSS-6 rating was limited since the start of the COVID-19 pandemic restrictions. However, the results of most correlations were similar to previous large-scale studies that have compared the CGI to the same psychometric scales using a stricter p value of < 0.001. Studies by Leucht et al. (2005a; 2005b; 2006) linking the CGI-S with the BPRS and PANSS found similar Spearman correlation coefficients between 0.4 – 0.74 despite important differences in population characteristics. Compared to our population of FEP outpatients, patients in these reports were in- and outpatients who were specifically recruited based on high severity of symptoms and selected measures were only rated weekly, at baseline and up to week 6 of treatment. Secondly, while the GAF served as one of the comparison measures for the CGI-S in capturing levels of

functioning, we are aware that it is not a pure measure of functioning, as the severity of symptoms –psychotic and negative symptoms – is also considered. Indeed, future studies should opt for the Social and Occupational Functioning Assessment Scale that is a more precise measure of functioning. Additionally, while the main stakeholders participated in this process, we did not collect qualitative information to understand their opinions on the CGI in practice. Thirdly, we did not present more fine-grained data that illustrates the usefulness of this approach in deriving indices of quality of care at the individual and/or the service levels. Furthermore, while this paper focused on the CGI-S, the measure of sensitivity to change using the CGI-I, is also an important aspect to capture as part of measurement-based care. These issues could not be addressed because of space limitations but will, however, be presented in a separate paper.

Despite these limitations, the present findings support the CGI-S as a valid and reliable tool that is feasible for clinicians to consistently use and thus suitable for MBC implementation in the context of a first-episode psychosis program. This study provides an important foundation on which to build upon while proceeding with the next steps of the proposed MBC implementation strategy. Having selected and evaluated the CGI, the next steps will be to use the ratings as a means to directly inform and improve pharmacological treatment algorithms in a manner that demonstrates to multiple stakeholders the relevant benefits of implementing MBC.

6. Conclusion

Though the benefits of MBC in psychiatry have been discussed for many years, MBC implementation – especially in the care of individuals with psychotic disorders – has been limited by a number of important barriers. This study described our initial approach to addressing the basic MBC implementation needs at a FEP program according to organizational barriers as outlined by Lewis et al. (2019). We focused on the engagement of stakeholders by selecting a simple, clinician-rated tool: the CGI. Following reliability and validity assessments of the tool, the CGI-S is simple to use and captures a global clinical picture similar to that of more sophisticated tools. The real-world context of our study coupled with findings of high interrater reliability and conformity to practice supports the feasibility of integrating the CGI-S into routine care. The findings of this

study have important implications for future implementation strategies of MBC in FEP care and in psychiatry.

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Chapter 4: Manuscript 2

Title: Measurement Based Care in a First Episode Psychosis program: development of an algorithm of care based on the Clinical Global Impressions Scale

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Abstract

Introduction:

Adherence to therapeutic guidelines in psychiatry is anchored and facilitated by rating scales. However, they are rarely used in routine care, particularly for psychotic disorders. Consequently, adherence to treatment guidelines are not ideal and patient outcomes are often sub-optimal. In this study, we used the clinician-rated Clinical Global Impressions Scale (CGI) to implement a measurement-based care (MBC) approach and derive indices of quality of care at a first episode psychosis (FEP) program.

Methods:

At the individual level, an algorithm was created using CGI scores and their changes over time to define the concept of Patient Requiring Clinical Attention (PRCA) that encompasses several categories (e.g. *episode of severity*, *treatment inertia*, or *treatment resistance*). At the service level, CGI scores were used to derive several indices of quality of care: severity of illness and its change over time, conformity to the use of low doses of antipsychotic medications, and clozapine offer index.

Results:

135 Patients were included in this study and 19 patients were identified as PRCA. The majority (63%) received timely medication. While, a minority (37%) were suspected cases of therapeutic inertia. Additionally, 15 patients met criteria for treatment resistance of whom 7 were offered clozapine (47%). At the service level, the average CGI improved by 2 points from baseline to month 1 and average doses of antipsychotic medications prescribed were in line with prescription guidelines for FEP patients.

Conclusion:

The proposed CGI-based treatment algorithm and service evaluation strategy can help to optimize quality care and services for patients.

Keywords: measurement-based care, first-episode psychosis, clinical global impressions scale

1. Introduction

Recovery, considered a primary goal in the treatment of schizophrenia, is a personal and multidimensional concept that involves both clinical (i.e., control of symptoms, regain of functioning) and experiential elements.

Remission is often defined in terms of symptomatic and functional improvement, usually in response to therapeutic intervention. In the context of psychotic disorders, response to antipsychotic medication has been defined differently (*treatment response, resolution, and remission of symptoms)* in different contexts (Kane et al., 2019). In clinical trials, treatment response is often defined relative to the baseline level of severity of symptoms (% reduction), as measured by specific rating scales (e.g., PANSS). In contrast, the concept of remission is defined in absolute terms and refers to a clinical state where the patient shows minimal symptoms. The Remission in Schizophrenia Working Group (RSWG) proposed that remission may be asserted if a severity score of "mild" or less is met for every one of the 8 core symptoms identified from multiple assessment scales (SAPS/SANS, BPRS, & PANSS) for a duration of 6 months or more.

The concept of resistance to antipsychotic medication often refers to a lack of response to antipsychotic medication (Kane et al., 2019). In schizophrenia, this concept is of paramount importance because it defines a group of patients (up to 30 %) that warrant treatment with clozapine, a medication reserved for patients who show resistance to other antipsychotic medications (Joober and Boksa 2010; Warnez & Alessi-Severini, 2014; Doyle et al., 2017). In terms of long-term benefits and quality of life, timely identification of treatment resistance and introduction of clozapine can be especially impactful for patients with first-episode of psychosis (Jones, 2013). In a recent review of the literature, Elkis and Buckley (2016) listed 6 different algorithms that were used to define resistance to antipsychotic medication, each using different scales, cut-offs of symptom severity and medication trials (with different types of medications and optimal duration of treatment and doses).

The variations in these definitions of response and resistance to treatment, along with the unpracticality of using complex and time-consuming assessment scales, is likely to result in

considerable inconsistencies in clinical practices, lack of adjusting treatments on a timely basis, tolerance of sub-optimal outcomes for long periods of times (therapeutic inertia), detection of treatment resistance and initiation of clozapine (Kane et al., 2003; Moore et al., 2007; Tandon et al., 2008), including for patients in their first-episode of illness (Lieberman et al., 2003; Agid et al., 2007), and ultimately impact rates of remission and recovery.

In addition to the multiplicity and complexity of algorithms, the implementation of these algorithms in clinical practice using an approach called Measurement Based Care (MBC), remains rare and poorly studied for individuals with psychotic disorders. Described as "the practice of basing clinical care on client data collected throughout treatment (Scott & Lewis, 2015)," MBC has been associated with better patient outcomes (e.g., increased remission rate, improved detection of treatment inertia, and higher rate of treatment response) compared with standard psychiatric care alone (Trivedi et al., 2006; Guo et al., 2015; Scott & Lewis., 2015; Fortney et al., 2017; Lewis et al., 2019).

In the field of mood disorders, large-scale MBC implementation studies such as the Texas Medication Algorithm Project for the treatment of Depression and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) have revealed enhanced pharmacotherapy outcomes such as minimized side effects and shorter time to remission. (Crismon et al., 1999; Trivedi et al., 2004; Trivedi et al., 2007). However, similar efforts for MBC implementation in the treatment of psychotic disorders have lagged behind for at least 2 reasons. First, diminished symptom insight associated with psychotic disorders prevent the use of convenient, patient-rated assessments (Thompson et al., 2001; Keshavan et al., 2004). Second, due to the complex and multidimensional nature of psychotic disorders, most MBC implementation studies have used a combination of multiple psychometric assessments that are not feasible to integrate into clinician routines (Chiles et al., 1999; Dinakaran et al., 2020). In face of these barriers, we used an MBC implementation approach based on the Clinical Global Impressions Scale (CGI), a brief, clinician-rated assessment that can be completed in less than a minute and has been previously validated for the assessment of psychotic disorders (Busner & Targum, 2007). Furthermore, because the rating of this scale is based on the overall clinical experience of the rater with schizophrenia, this scale

is considered to have an intuitive and clinically meaningful significance (Nierenberg & De Cecco, 2001; Busner & Targum, 2007).

In a previous paper, we evaluated the reliability, validity, and feasibility of the CGI for MBC implementation in the context of FEP care (Khau et al., 2021). The findings demonstrate that CGI ratings are reliable and reflect a clinical picture similar to the combination of more sophisticated scales while being comparably brief. Importantly, we have also shown that the majority of clinicians completed the CGI-S rating at most encounters with their patients, which is essential for an adequate implementation of MBC (Lambert et al., 2001; Lewis et al., 2019).

In this manuscript we aim to illustrate how this MBC approach based on the CGI can be used to provide clinically meaningful and actionable feedback by deriving indices of quality of care at two levels:

1) Patient-level: CGI criteria can be used to facilitate the implementation of an algorithm to improve decision-making and timely adjustment of pharmacotherapy, including the prescription of clozapine.
2) Service-level: aggregate CGI data can be used to evaluate patient improvement over time and help in assessing the adherence of a FEP program to particular recommendations of treatment guidelines in FEP (e.g. low dose antipsychotics)

2. Methods and Measures

2.1 Setting

This study was conducted in the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal), a community-focused, clinical academic program aimed to provide comprehensive medical and psychosocial treatment to young individuals experiencing their first episode of psychosis (FEP). Participants included in this study were between 16 and 35 years of age, diagnosed with either affective or non-affective psychosis and who have received antipsychotic medication for no more than thirty days total in their lifetime.

The CGI was introduced to PEPP in 2017 as a clinician-rated scale. Four sessions were offered to the clinicians to familiarize them with the scale and to conduct inter-rater reliability measures (roughly 6 months apart between January 2017 and September 2019). The first session included a basic introduction of the CGI along with a patient vignette for clinicians to rate. Subsequent sessions included a shorter "refresher" presentation of the CGI along with different patient vignettes to continuously assess interrater reliability. Additionally, clinicians were asked to include CGI ratings on clinical notes during each evaluation with patients as regularly as possible. This study utilizes this previously collected CGI data recorded between January 2017 and September 2019 and only includes patients that had at least three consecutive CGI ratings done between their month 1 to 24 evaluations. As such while 337 patient files were available, only 135 were included in the study sample.

The research protocol has been approved by the Ethics Committee of the Douglas Hospital. All patients participating in this study provided written and informed consent.

2.2 The Clinical Global Impressions Scale for MBC Implementation

The Clinical Global Impressions Scale (CGI; Guy, 1976) was selected for its well-validated and quick-to-administer ratings. It is composed of two, single-item subscales: 1) a measure of global symptom severity at the time of evaluation (CGI-S) taking into account effects on distress levels and functioning, and 2) a measure of global improvement since baseline (CGI-I). Both subscales are rated on a scale of 1-7 with intuitive anchor points and provide simple, readily understandable measures of patient severity of illness and progress in routine clinical practice (Nierenberg & De Cecco, 2001; Leucht et al., 2005; Busner & Targum, 2007). While the CGI can be used in the context of any psychiatric disorder, in a previous study, the CGI was specifically evaluated to be reliable, valid, and feasible for routine clinical use in our first episode psychosis program (Khau et al., 2021).

2.3 Derivation of a CGI-based Treatment Quality Detection Algorithm, for Use at the Individual Patient Level

At the patient level, a primary benefit of MBC in pharmacotherapy is the optimization of treatment decisions and ultimately improved outcomes. However, this hinges on the timely

detection of a lack of expected treatment response and flagging this to the clinician for adjustment. As such, the treatment quality detection algorithm (Figure 1) developed in this study addresses three issues of clinical concern related to poor patient treatment response that could be flagged to the treating clinician.

The first issue of clinical concern is the identification of Patients Requiring Clinical Attention (PRCA) due to early poor treatment response to medication. Using CGI criteria, PRCA was defined as *"at least 2 consecutive visits of CGI-S ≥3 (minimally ill) and CGI-I ≥4 (no change)."* PRCA status was verified through examination of prescription history and clinical notes of patient evaluations. Subsequently, PRCA status was confirmed through agreement between two clinicians and a research assistant. The CGI criteria for PRCA were informed by two studies that used the CGI to operationalize treatment-resistance and treatment response. The CGI-S cut-off of 3 (minimally ill) was informed by a clozapine efficiency study by Kane et al. (1988) whereby treatment-resistance was operationalized as a "minimum CGI-S of 4 (moderately ill)." However, in the Kane et al. study, participants were patients with chronic schizophrenia. In consideration for the medication sensitivity of our FEP population, we used a more stringent CGI-S criterion of 3. The CGI-I criterion of 4 was chosen based on the associated anchor point of "no change" as well as the findings from a Stentebjerg-Olesen et al. (2013) study on the early detection of non-response to antipsychotic medication in a youth population diagnosed with a schizophrenia spectrum disorder. Their sample population closely resembled ours as they were mostly treatment-naïve or had not taken more than 1 antipsychotic. The findings of this study demonstrated that a CGI-I of 4 within the first month of treatment was a significant predictor of non-response later in treatment. Upon algorithm detection, PRCA status was subsequently confirmed through clinician notes in the patient's file and agreement between two clinicians.

The second issue of clinical concern is determining if the clinician remarked on and addressed the lack of treatment response. Clinician action was evaluated based on medication intervention during the 2 months following the high CGI ratings. For the purpose of this study, action is defined as: any increase or decrease in antipsychotic dose as well as any removal or addition of antipsychotic medication. Based on the presence of clinician action by month 3, patients were placed into 2 categories: episode of severity (ES), if the patient continued to meet PRCA criteria

in spite of psychiatrist action or potential therapeutic inertia (TI) if action was not taken and the patient continued to meet criteria for PRCA. While TI is a term that is rarely used in psychiatry, it is often used in the management of other chronic diseases to signify stagnation of patient progress in treatment. TI is an impediment to remission and is defined by Phillips et al. (2001) as "recognition of the problem, but failure to act." However, this failure to act can be attributed to several sources thus, TI was further divided into: patient-related, clinician-related, or other. In our context of MBC implementation, we reasoned that the identification of therapeutic inertia in a patient, once signalled to the clinician would prompt an adjustment of the treatment or a documentation of the reasons for lack of action.

The third issue of clinical concern is the identification of possible treatment resistance. In this context, treatment resistance is defined in terms of a patient's response to pharmacological treatment over time. The main purpose of this subcategory is to define and flag, at early stages, patients who are potentially resistant to treatment and could be candidates for clozapine. Clozapine is indicated when a patient has not responded to 2 antipsychotics (of which at least one is atypical) at adequate doses for 4-6 weeks (Elkis & Buckley, 2016). Thus, in consideration of this guideline, we propose novel criteria for suspected treatment inertia and clozapine initiation in FEP which includes: 1) patients who experienced 2 or more instances of ES or 2) patients who experienced TI (>8 weeks of high CGI ratings) after 2 or more trials of antipsychotics. These criteria may seem slightly stringent, however, early use of clozapine for individuals with FEP experiencing persistent symptoms has been associated with benefits including rapidly improved treatment response and increased likelihood of achieving symptomatic remission (Edwards et al., 2011).

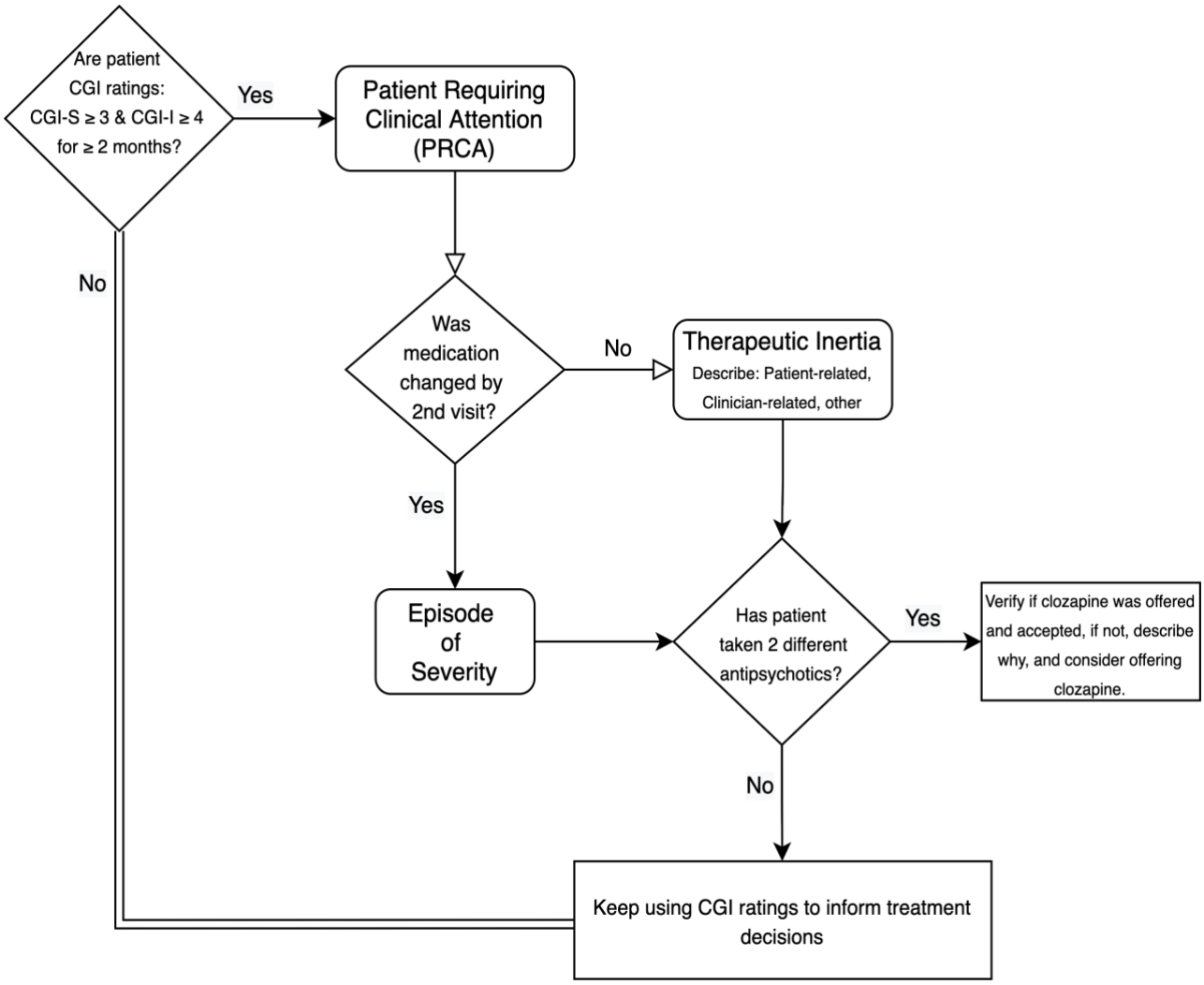

Fig.1 CGI-based Treatment Quality Detection Algorithm. Patients who had 2 consecutive months of CGI-S ≥3 (minimally ill) and CGI-I ≥4 (no change) were categorized as patients requiring clinical attention (PRCA). Following PRCA categorization, prescription history was consulted to verify whether the clinician made any changes to medication. If a change was made, the 2-month period was considered an episode of severity. However, if no changes were made, the patient was sub-categorized as having experienced potential therapeutic inertia. Medication history of both subgroups of PRCA (therapeutic inertia and episodes of severity) were verified for clozapine criteria of having tried 2 different antipsychotics. If patient met criteria, their files were further verified for an offer of clozapine. CGI-S = Clinical global impressions scale of severity of illness; CGI-I = Clinical global impressions scale of improvement

2.4 Derivation of Service- Level Indices of Care

The primary goal of antipsychotic medication is the control of psychotic symptoms and to facilitate recovery. It is therefore important that one of the primary indices of quality of care (IQC), at the service level, reflects overall patient improvement through reduction in severity of illness with antipsychotic use over time. This index can be easily tracked using average CGI-S scores over time, since ratings are anchored in such a way that a one-point reduction of the CGI-S is considered clinically significant.

Once symptoms are controlled, the secondary goal for pharmacotherapy is to minimize the harm associated with medication side effects. Thus, another IQC at the service level of FEP care, is applying a minimal effective dose strategy as recommended by treatment guidelines (International Early Psychosis Association Writing Group, 2005). This recommendation is based on extensive literature that has demonstrated the heightened sensitivity to antipsychotics and increased risk for extrapyramidal side effects in FEP populations (Remington et al.,1998; Masi & Liboni, 2011; Haddad et al., 2012). However, without standard assessments and quantitative guidelines in practice, it is not uncommon for patients to be prescribed doses that exceed these recommendations (Sernyak & Rosenheck, 2007; Roh et al., 2015). In this study an IQC for use of minimal effective antipsychotic dose was defined using two metrics. First, the average dose of antipsychotic medications received by patients treated in the clinic (calculated in olanzapine equivalents) was compared with recommended dosing for this patient population. Secondly, the effectiveness of this average dosing was judged against the average level of severity of illness in our patient population, measured using the CGI-S.

3. Statistical Analyses

Chi squared tests were computed to establish goodness of fit between demographics of the sample population and the general population at PEPP-Montreal.

At the service level, overall decrease in CGI-S and CGI-I scores over 24 months was used as an indication of patient improvement over time and an indication of quality of care at PEPP. Average CGI-S and average CGI-I per month were calculated for all patients between January 2017 and

September 2019. Unlike the sample population for patient-level analyses, individuals were included regardless of whether they had 2 consecutive months of CGI-S and CGI-I. CGI trends during the 24 months of treatment were then plotted. Given that a 1-point change on the CGI is considered to be clinically and statistically significant (Leucht et al., 2005; 2006) a simple visual inspection of this data is sufficient to reflect the evolution of treatment over time.

In addition to patient improvement, adherence to FEP guidelines for the prescription of low dose antipsychotic was verified by first converting all antipsychotic medications to Olanzapine equivalent doses. Olanzapine equivalencies were calculated using the Olanzapine to antipsychotic ratios defined by Leucht et al. 2020. Average olanzapine-equivalent doses were then calculated per month for each of the consecutive 24 months. We also compared the CGI-S, CGI-I ratings as well as the Olanzapine doses between the PRCA *vs.* the overall study population using t-tests (assuming unequal variance) computed with SPSS.

4. Results

A total of 135 patients had at least three consecutive CGI-S and CGI-I ratings done between their month 1 to 24 evaluations and were included in the study. There were no statistically significant differences in terms of patient demographics between this sample and the overall patient population at the clinic (Table 1). The majority of the sample were male (66%), age ranged from 16 – 35, average age was 24 $\pm$ 5.03 years and most patients had a diagnosis of non-affective psychosis (62%).

Table 1. Demographics characteristics of study sample compared to the overall clinic population

Demographic Characteristics	Study Sample[*‡]	Clinic Population[*§]
Mean age of onset, years **(SD)**	24.7 *(5.03)*	24.41*(5.26)*
Gender (%)		
Male	62%	64%
Female	38%	35%
Diagnosis (%)		
Affective Psychosis	34%	34%
Non-Affective Psychosis	66%	66%

[*]All characteristics were not statistically significantly different ($p \leq 0.05$) *between the two populations*
[‡] Study Sample n = 135
[§] Clinic population n = 337

4.1 Quality of Care at the Patient Level

At the individual patient level, using the CGI-based treatment quality detection algorithm described in Methods (section 2.4), 19 patients were identified to be PRCA at one time or another during their follow-up, which represents roughly 14% of the sample population. Two out of the 19 patients were also identified to have experienced both severity episodes and therapeutic inertia. Including these two cases, a total of 21 PRCA were identified, of which 14 (10.4% of the sample population) were severity episodes and 7 (5.1% of the sample population) were therapeutic inertia. PRCA rated both clinically and statistically significantly higher than the sample population on the CGI-S and CGI-I while taking comparably lower doses of medication (Table 2).

Table 2. Average CGI and antipsychotic dose taken by patients identified to be PRCA compared to overall sample population

Averages	PRCA‡	Study Sample§
Average CGI throughout 24 months of treatment	CGI-S: 3.3* ± 0.80 CGI-I: 3.8 ± 0.87	CGI-S: 2.3* ± 0.27 CGI-I: 3.4 ± 0.27
Average CGI during months of episode of severity	CGI-S: 4.2** ± 0.83 CGI-I: 4.4** ± 0.46	CGI-S: 2.5** ± 0.13 CGI-I: 3.2** ± 0.15
Average antipsychotic dose**	6.49mg	7.10mg

CGI-S = Clinical global impressions scale of severity; CGI-I = Clinical global impressions scale of improvement; PRCA = patients requiring clinical attention

*Statistically significantly different $p < 0.05$

‡ PRCA n = 19

§ Study Sample n = 135

**Olanzapine equivalent dose based on reported equivalents by Leucht et al., 2020

The categorization of PRCA into suspected therapeutic inertia and severity episode subgroups are detailed in Table 3. Including the 2 cases with both severity episodes and therapeutic inertia, most (n = 14) met the criteria for having experienced a severity episode compared to therapeutic inertia. Out of the 7 patients who met the criteria for therapeutic inertia, 3 were considered as patient-related and 4 clinician-related.

Table 3. Subgroup of PRCA who experienced a period of therapeutic inertia or episode of severity

PRCA subgroup	PRCA[‡*]	PRCA /Total study sample (%) [§]
Therapeutic Inertia	7	5.1%
Patient-related	3	2.2%
Clinician-related	4	3.0%
Episode of Severity	14	10.4%

PRCA = Patients requiring clinical attention
[*]2 patients who experienced double cases (both therapeutic inertia and episodes of severity) were considered twice, once per sub-category
[‡] Number of PRCA instances n = 21
[§] Total study sample n = 135

4.1.2 Clozapine offer

Using our treatment resistance criteria, 9 severity episode cases and 6 therapeutic inertia cases met the criteria for potential clozapine indication. The presence of clinician intention to initiate clozapine as well as the patient's acceptance of the offer of clozapine (as documented in the patients' files) was as follows: 15 out of 19 PRCA met criteria for potential treatment resistance. Out of these 15, clozapine was offered and accepted by 3 (20%), offered and refused by 4 (27%), and not offered to 8 (53%).

4.2 Quality of Care at the Service Level

Average CGI-S ratings of PEPP patients are shown in Figure 2. Average baseline CGI-S is slightly over 5 – "markedly ill" and notably declines within the 1st month of treatment to 3 –

"mildly ill." Average CGI-S from baseline to month 24 is between 3 and 2. Ratings are reported as integers to reflect the rating structure of the CGI-S.

Antipsychotic dose taken throughout treatment at PEPP was on average, an Olanzapine-equivalent dose of 6.49 mg. This is below the minimum effective dose of 7.5 mg and well below the target median dose of 10-20 mg (Leucht et al., 2020). These low doses, along with low levels of severity of illness strongly suggest that the program is following the recommendation of minimally effective doses of anti-psychotic medications.

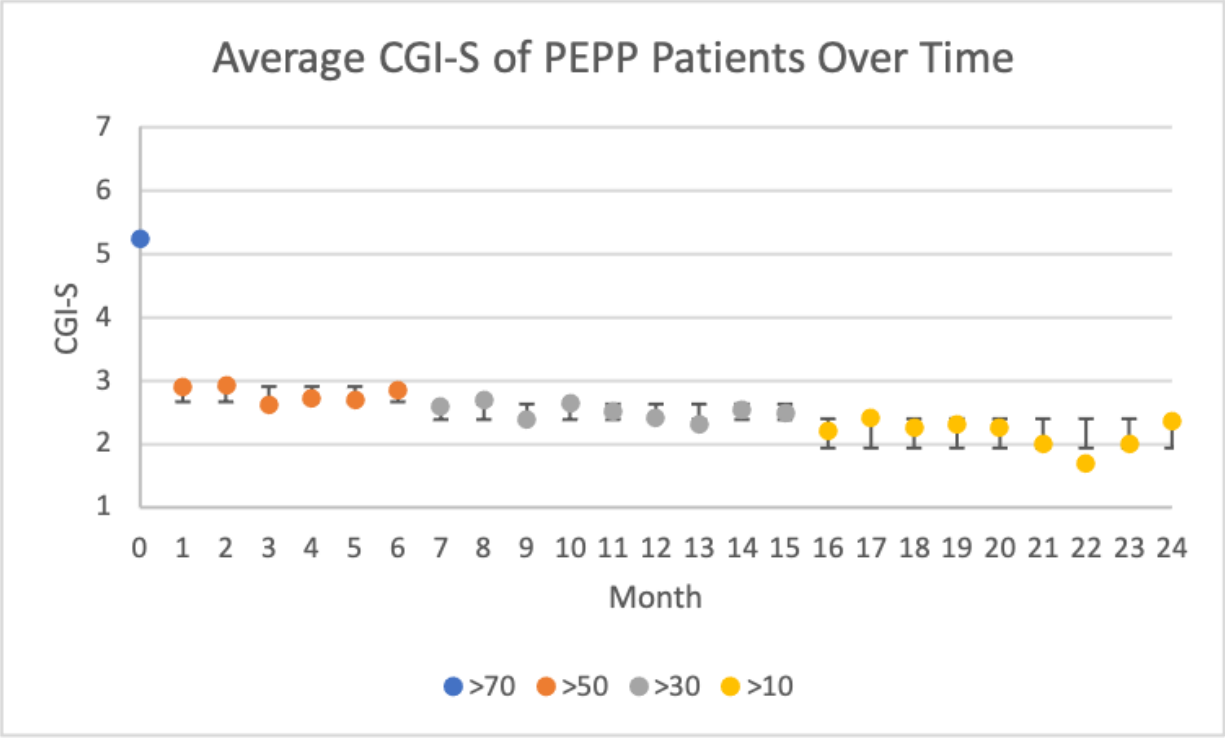

Fig. 2 Average CGI-S of patients at PEPP per month over 24 months with standard deviation. Colours represent varying sample sizes for which CGI ratings were available.

CGI-S = Clinical global impressions scale-severity of illness rating; PEPP = Prevention and early intervention program for psychosis.

5. Discussion

In the present study, we provide data on how the CGI can be used for measurement-based care to address a number of limitations in the quality of care for individuals with psychotic disorders at the individual and service levels of care.

5.*1 Individual-Level Indices of Quality of Care*

While treatment algorithms in schizophrenia outline criteria for treatment response and resistance and may help the clinicians to adjust medications, they require important, and possibly unrealistic, efforts of documentation for busy clinicians, particularly in under-resourced settings. Furthermore, these classical algorithms are primarily intervention-focused guidelines that do not permit dynamically flagging patients in need of attention prior to fulfilling non-response criteria. Considering these limitations, we used CGI criteria to operationalize and introduce novel definitions of *treatment inertia* (TI) and *potential treatment resistance* through the proposed concept of Patients Requiring Clinical Attention (PRCA). Additionally, we propose novel criteria for considering clozapine prescription with first episode psychosis populations. Weaving these concepts into a simple algorithm that can be integrated in the day-to-day practice of clinicians, this treatment quality detection tool allows timely decision-support and identification of patients who are not responding ideally to treatment. This may help personalize treatment, reduce risk for therapeutic inertia, and draw attention to some patients who may present severe or resistant forms of illness. The algorithm efficiently identified cases of PRCA, which included instances of potential TI where patients received no pharmacological intervention despite not improving. Importantly, this algorithm provided a simple means of identifying patients who could have benefitted from clozapine and could potentially provide a simple means of improving clozapine prescription rates for individuals who are treatment-resistant.

5.*2 Service-Level Indices of Quality of Care*

As suggested by Scott & Lewis (2015), the ability to have a simple assessment of services can allow downstream benefits in terms of budgeting and resource allocation. In this paper, we proposed three indices of quality of care at the service level.

First, the average level of improvement as measured by the CGI-S score over time: the average level of CGI-S dropped from 5 to 3 in the first month and was around 2 and the end of the treatment. These numbers are excellent indication of program quality of care.

Second, we calculated the average dose of antipsychotic medication used at each month and verified conformity to FEP treatment guidelines, namely the prescription of antipsychotics in low but effective doses, as a means of minimizing side effects in this sensitive population. By establishing that patients were significantly improving over time and receiving relatively low doses of antipsychotic medications, our metrics indicated that the FEP program was performing well and was compliant with FEP treatment guidelines. Third, we estimated the number of patient who are potentially resistant to antipsychotic medication and who were offered clozapine. Only 47% of patients who met the criteria for potential resistance to antipsychotic medication were offered clozapine. Although the absolute numbers are small, this is a clear indication that more efforts need to be deployed to improve this clozapine offer index.

While we presented three indices of quality of care at the service level , using this approach of MBC can help deriving additional IQC at the service level based on our proposed individual-level indices. For instance, it is possible to average the length of episodes of therapeutic inertia (categorized into patient or clinician related) for all patients which will provide insight on opportunities for service improvements.

5.3 Limitations

Some limitations should also be considered when interpreting the results of the present study. First the sample size available was quite small, because the treatment detection algorithm was applied to patient files that were open during the initial phase of CGI implementation, when ratings were less regularly completed. However, for the purpose of this study, the sample size was sufficient to demonstrate the simplicity of the algorithm and feasibility of its use. Additionally, the proportion of cases we identified as potentially treatment resistant and needing clozapine are consistent with findings from previous studies that have investigated treatment resistance in first episode psychosis populations (Demjaha et al., 2017; Bozzatello et al., 2019). Secondly, the sub-categorization of TI cases into patient, clinician, and other reasons were tentatively completed through consensus

between two psychiatrists and a research assistant and informed by thorough examination of clinical notes in the files. However, the categorizations should be validated with the primary psychiatrist of each patient.

6. Conclusion

In conclusion, we have proposed a framework for the integration of measurement-based care (MBC) at the individual and service levels of care using the Clinical Global Impressions Scale. At the individual level, we have created a CGI-based treatment quality detection algorithm which operationalizes treatment progress indices (e.g. response) within the concept of 'patient requiring clinical attention' and outlines novel criteria for potential treatment resistance that could optimize adherence to clozapine prescription guidelines. This algorithm demonstrates the potential of allowing previously reported MBC benefits such as more efficient progress tracking, timely and personalized adjustment in medications, as well as early identification of treatment resistance and the prescription of clozapine. At the service level, aggregate CGI data permitted insight and extraction of indices of quality of care at our first episode psychosis program including patient improvement (e.g., CGI-S & CGI-I from baseline to month 24) and monitored adherence to FEP guidelines of low-dose antipsychotic prescription. Overall, the proposed applications of the CGI could improve MBC integration and facilitate implementation for the care of individuals with psychotic disorders.

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Chapter 5: Thesis Discussion & Conclusion

While measurement-based care and its core components of systematic treatment tracking and measurement-informed treatment decisions are routine in psychotic disorder research, its implementation in clinical practice has lagged behind. As such, the aim of this thesis was to address this gap and devise a strategy for measurement-based care implementation at a first episode psychosis program. This was accomplished in two phases: 1) evaluation of the Clinical Global Impressions Scale in terms of suitability for MBC within our context of care and 2) the development of a CGI integration strategy to allow MBC implementation that would derive indices of quality of care at the individual and service levels.

5.1 Evaluation of the Clinical Global Impressions Scale

Being one of the only clinician-rated tools that require less than a minute to complete, the CGI was selected primarily for its objective simplicity. Further evaluation of the symptom severity assessment item of the CGI (CGI-S) provided additional evidence in support of the CGI as a suitable measure on which to base MBC at our FEP program. Indeed, the CGI-S was shown to be feasible for clinician use in their everyday routines as demonstrated by a high fidelity of practice in terms of rating completion among psychiatrists who saw the most patients. Although fidelity of practice fluctuated and was significantly lower for psychiatrists who saw fewer patients, this was an expected, natural lag in adoption of novel practices that should improve over time. Additionally, a good interrater reliability was found when psychiatrists were asked to rate the CGI without previous training. This suggests that the CGI rating scale is intuitive for clinicians as suggested by the literature (Nierenberg & De Cecco, 2001; Leucht et al., 2005b; Busner & Targum, 2007). Finally, this single measure reflected a comprehensive clinical picture of the patient that was comparable to the combination of multiple well-validated assessment scales for psychotic disorders. However, individually, negative symptoms were not captured as well as positive symptoms and symptoms of functioning interference. This information will be fed back to the clinicians and another assessment of concurrent validity will be conducted. It is noteworthy that previous research has shown a good correlation between the CGI and PANSS negative symptom items (Leucht et al., 2019). Taking these results and considerations together, we decided to move forward with the CGI as the measure on which to base MBC implementation at our program.

5.2 Strategy for MBC implementation:

Having selected a measure for systematic treatment tracking, we developed a strategy to meaningfully integrate the CGI at the individual (clinician & patient) as well as the service levels of care. At the individual level, we proposed the concept of Patients Requiring Clinical Attention (PRCA) and developed a treatment decision-support algorithm for clinicians using CGI criteria to operationalize and present a novel definition of *treatment inertia* and signs of *treatment resistance.* This algorithm was feasible for clinical use and efficiently identified, retrospectively, 19 patients (14%) as PRCA of whom majority (n = 12) received pharmacological intervention. While 7 PRCA (5%) did not receive timely intervention and were categorized as having experienced treatment inertia. Moreover, 8 out of 15 patients who met criteria for treatment resistance were not offered clozapine. While this ratio is slightly higher than the 30% that is usually reported of patients who are not on clozapine despite meeting requirements (Latimer et al., 2013; Warnez & Alessi-Severini, 2014), it does reflect the reality that clozapine is under-prescribed and our program is no exception. However, our algorithm and proposed criteria for *treatment inertia* and *potential resistance* could optimize and standardize prescription adherence to best prescription practices and guidelines for agents such as clozapine. Moreover, this could feed back into the evaluation of service-level quality of care indices such as the average duration of treatment inertia and the percentage of patients who were not offered clozapine despite being identified to be potentially treatment resistant.

Additionally, at the service level, CGI ratings showed that patients were indeed improving over time while taking antipsychotic doses in line with FEP guidelines. This sequential monitoring of patient progress prior to verification of low-dose antipsychotic is important since, interestingly, we found that PRCA had higher CGI ratings than the sample population while taking comparably lower doses of medication. As such, aggregate CGI ratings provided an easy way not only to track treatment progression over time but also to monitor prescription of low dose antipsychotics as per FEP guidelines.

5.3 Limitations:

This thesis has a number of limitations. Firstly, the sample sizes were relatively small for both studies. In the first study, the collection of the PANSS-6 ratings was limited since the start of the COVID-19 pandemic restrictions. However, our findings on concurrent validity of the CGI-S reflected previous studies with larger samples (Leucht et al. 2005a; 2005b; 2006). In the second study, the sample size was limited due to retrospective application of the treatment detection algorithm to patient files that were open during initial phase of CGI implementation, when ratings were less regularly completed. However, the sample size was sufficient to demonstrate the simplicity of our algorithm and feasibility of its use. Additionally, the proportion of cases we identified as potentially treatment resistant and needing clozapine are consistent with findings from previous studies that have investigated treatment resistance in first episode psychosis populations (Demjaha et al., 2017; Bozzatello et al., 2019). Another limitation is the lack of clinician input, which could have provided valuable insight into certain specific issues, in both studies. While we computed clinician fidelity of practice as a proxy measure of measurement feasibility in the first study, we did not collect qualitative information to understand their opinions on the CGI in practice. Additionally, in the second study, the sub-categorization of treatment inertia cases into patient, clinician, and other reasons were tentatively completed through consensus between two psychiatrists and a research assistant and informed by thorough examination of clinical notes in the files. Future studies should collect qualitative data on clinician opinion of the CGI in order to inform better integration of the tool in practice and treatment inertia sub-categorizations should be validated with the primary psychiatrist of each patient.

5.4 Future Directions: Digitalization and a Learning Health Care System

While we applied the treatment decision-support algorithm to retrospectively evaluate quality of care, we expect to prospectively apply this algorithm in practice to allow dynamically flagging patients who might need more clinical attention. Importantly, our approach will be based on the concept of Learning Health Systems (LHS). Building on the idea that health systems are dynamic systems that generate information through clinical practice and research, a LHS integrates research-generated information in real practice and tests its impact on the various outcomes. Outcome information is then used to inform research for further improvement (including eliminating practices that turn out not to be effective) at each cycle of implementation (Figure 1;

Committee on the Learning Health Care System in America, 2013). As such, future directions will focus on a more systematic collection of data as well as the digitalization and prospective use of the CGI algorithm that will flag patients as PRCA in real time and prompt clinicians to take action throughout treatment. Following the philosophy of a LHS, the aim will be to promote a culture for the use of this tool which will allow for the continuous collection of data. The data collected will subsequently be analyzed and used for the recalibration of the tool and/or additional clinician training to improve the homogeneity and accuracy of ratings. Ultimately, this will feedback into improving the quality of care received by patients.

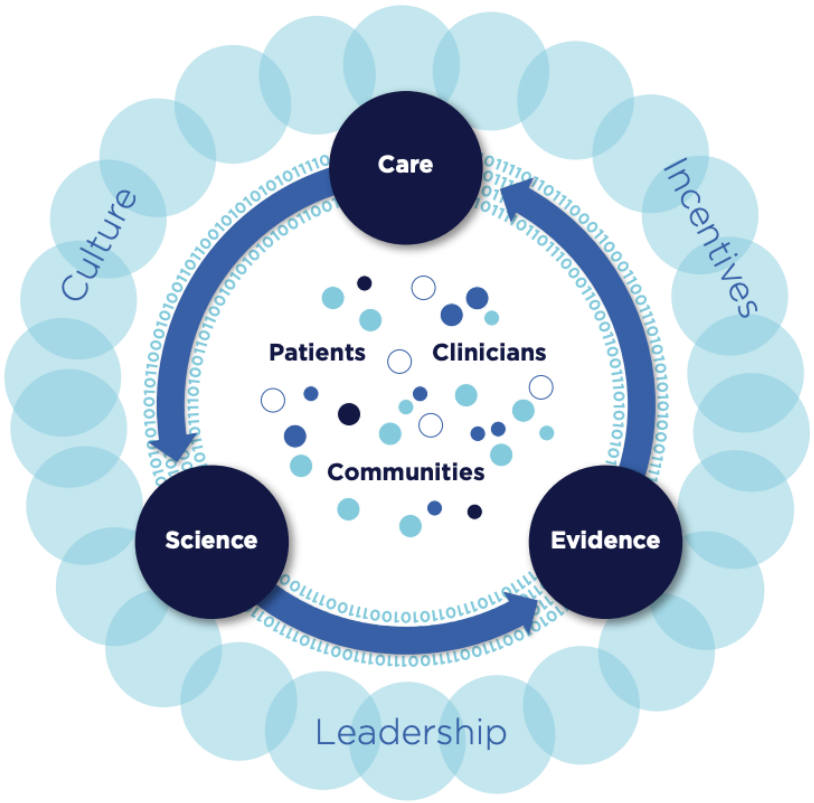

Fig 1. Committee on the learning health care system in America (2013). *Best care at lower cost: the path to continuously learning health care in America*.

Conclusion:

A major barrier to measurement-based care implementation within the context of psychotic disorders has been the selection of a suitable measure. The Clinical Global Impressions Scale, a measure that takes less than a minute to rate, could potentially overcome this barrier and bridge the gap towards MBC implementation for the care of individuals with psychotic disorders. In this thesis we have demonstrated that the CGI-Severity of Illness assessment is not only a valid global assessment of psychotic symptoms but also a reliable, intuitive, and feasible measure for routine clinician use. In combination with the CGI-Improvement rating, CGI criteria can be used to define circumstances when patients are not responding optimally to treatment. These criteria can be meaningfully integrated into a decision support algorithm for clinicians to prevent treatment inertia and promote adherence to pharmacological prescription algorithms such as clozapine. Moreover, aggregate CGI ratings and can be used to evaluate quality of care at the service level and ensure monitored prescription of low dose antipsychotics according to FEP guidelines. Overall, the CGI, integrated according to an MBC approach is a powerful accessory to care and has the potential to nudge forward MBC implementation progress within a context where it has lagged behind.

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