Medication exposure in highly adherent psychiatry patients

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Abstract

Medication exposure is dependent upon many factors, the single most important being if the patient took the prescribed medication as indicated. To assess medication exposure for psychotropic and other medication classes, we enrolled 115 highly adherent psychiatry patients prescribed five or more medications. In these patients, we measured 21 psychotropic and 38 non-psychotropic medications comprising a 59-medication multiplex assay panel. Strict enrollment criteria and reconciliation of the Electronic Health Record medication list prior to study initiation produced a patient cohort that was compliant with 91% of their prescribed medications as determined by comparing medications detected empirically in blood to the EHR medication list. In addition, 13% of detected medications were not in the EHR medication list. We found that only 45% of detected medications were within the literature-derived therapeutic reference range; the majority were detected at concentrations outside of this range, with 40% below and 15% above the reference range specific to each medication. When psychotropic medications were analyzed at trough-level, only sertraline was found to be within the therapeutic reference range for all patients tested, with concentrations of the remaining medicines indicating extensive sub-therapeutic exposure. This is the first study to empirically and comprehensively assess medication exposure obtained in highly compliant, co-morbid patients, minimizing the important behavioral factor of adherence known to drive erratic medication exposure. These data indicate that sub-therapeutic exposure is extensive and must be considered when therapeutic issues arise, such as treatment resistance in psychotherapy.

Key words: Adherence, Medication Therapy Optimization, Polypharmacy, Precision Medicine, Therapeutic Drug Monitoring, Treatment Resistant Depression, Treatment Resistant Psychosis

Introduction

Poor medication adherence is often associated with poor outcomes in disease, including depression and psychosis[1-2]. Improving medication adherence using a variety of intervention strategies can improve patient outcomes, demonstrating the importance of taking prescription and over-the-counter medications as prescribed[3]. However, individuals that take medications at the prescribed dosage are often refractory to treatment, so proper adherence does not guarantee therapeutic response[4-6]. Adherence behavior in patients is not black or white, but rather lies on a continuum. At one extreme, medications are not taken by patients at all, and therefore cannot be detected in the patient with any type of monitoring. More typical is partial adherence, when a medication is not taken at the proper dosage, dosage interval, or in a sustained manner, all three of which are important factors in determining if medications reach or exceed required levels to produce the intended therapeutic effect. Although frequently studied as the sole factor in treatment outcomes, adherence is not the only determinant of medication exposure.

The exposure of each medication that a patient takes and the likelihood that it will reach a sustained therapeutic concentration is impacted by multiple intrinsic (i.e. genotype, hepatic function) and extrinsic (i.e. diet, concomitant medicines) factors, making exposure difficult to predict and highly variable in individual patients. Intrinsic and extrinsic variables that drive medication exposure are rarely measured in clinical practice, but when they are, can be leveraged to improve dosing. For example, consideration of pharmacogenetic parameters in the optimization of psychotropic medication choice and dosage has been shown to improve outcomes in depression [7-9]. Other examples include hepatic function, drug interactions, and diet for single therapeutic indications[10]. For co-morbid patients treated with complex drug regimens, however, pharmacodynamic and pharmacokinetic drug interactions may result from polypharmacy. Therefore, understanding the concentration and types of concomitant medications are parameters that must be considered when optimizing overall medication therapy. Clearly, adherence is the most important factor in exposure, but to improve therapy for the individual patient, there is a need to move from dosage-based prescribing to quantitative methods that consider the variability in how each individual patient will respond to each administered medication. These concepts underlie the Precision Medicine Initiative[11-12].

Frequent changes in medication therapy, lack of persistence, and complications arising from the use of different electronic health records (EHRs) by multiple prescribing physicians are all reasons that medications taken by the patients might not align with the medical record that prescribers are working from[13-14]. In addition, although discontinuation of medication therapy by the patient would not manifest in the medical record this behavior would be reflected in empirical measures of medication levels in blood. Inconsistent adherence or lack of persistence would lead to sub-therapeutic medication exposure, sub-therapeutic response, and ultimately sub-optimal outcomes. Most medications used to treat psychiatric disease reach steady state blood concentrations when taken at the recommended dosing schedules, therefore, measurement can be used to determine if the right amount of medicine is being received by the patient[15-16]. Insufficient medication exposure that results in blood concentrations below therapeutic ranges have no proven therapeutic benefit, and therefore would drive unnecessary costs for the patient and healthcare system. Although

medication mismanagement costs the US Healthcare System $200 billion annually[17-19], the cost of sub-optimal disease treatment has not been quantified.

Therapeutic drug monitoring is a proven and effective means to optimize treatment for medications with narrow safety margins[16]. When aligned with the EHR medication list, therapeutic drug monitoring data offers an empirical measure of adherence and medical record accuracy[20]. Further, medication monitoring performed in a quantitative biological compartment, such as serum or plasma, can be used as a surrogate of medication efficacy, as blood levels typically mirror target engagement[21-22]. Technological advances now allow for multiplex medication measurement in a single sample, which could afford the healthcare provider a window into every medication in the patient and its blood concentration at a point in time. This approach would be particularly useful for psychotropic medications where concrete biomarkers of efficacy are scarce, therapeutic reference ranges are well established, and resistance can occur [15]. Treatment resistance to antidepressant and antipsychotic medications is common[23-25], and has been linked in at least some instances to medication non-adherence and sub-therapeutic exposure[26] , but also raises the question as to how other factors that impact drug exposure might contribute.

In the current study, we measure adherence empirically with a multiplex assay that quantitates 59 psychiatric and non-psychiatric medications in a cohort of psychiatric patients taking multiple medications, allowing an unprecedented view of medication levels in the polypharmacy patient. Because the prospective study design selected for highly adherent patients with medical records that were reconciled prior to enrollment, we were able to investigate the manifestation of exposure variability for multiple medications simultaneously in patients that took their medications largely as prescribed. We find variable exposure relative to expected blood levels for both psychiatric and non-psychiatric medications administered at standard doses, and that sub-therapeutic exposure was common. Therefore, quantitative measures of medication concentrations must be factored into medication therapy management if we are to truly personalize medication therapy in the complex patient.

Results and Discussion

We have previously shown that adherence, as defined by comparing empirically detected medications with those in the EHR medication list, is higher in prospectively enrolled clinical trial patients than in patients where medications were measured without prior notification of testing[20] . In the present study, we created a highly adherent, prospectively enrolled patient cohort to determine if psychotropic medication taking behavior differed from non-psychotropic medication taking behavior, and whether psychotropic medications taken by patients as prescribed by physicians were detected at concentrations within published therapeutic reference ranges.

The present study included 115 prospectively enrolled patients entering the Cleveland Clinic Department of Psychiatry and Psychology. On average, patients were prescribed 4.3 panel medications based upon the EHR medication list and had 4.0 panel medications empirically detected in their blood. For 65 patients (57%), the actual medications detected differed from those in the EHR

medication list due to patient non-adherence or the use of medications not listed in the EHR (over-the-counter and/or prescription medications; Table S2). The average patient age was 57 years, and consistent with enrollment criteria, all patients were co-morbid as determined by taking medications from multiple medication classes. Summary patient characteristics and medication parameters are presented in Table 1.

Table 1: Characteristics of psychiatry patient cohort and summary results

Total patients	115
Female patients	90 (78%)
Age range	23-81
Average age	57
Prescribed meds per patientt [a]	
Range	1-10
Average	4.3
→ of which detected [b]	3.6
Detected meds per patientt	
Range	0-10
Average	4.0
→ of which not in EHR [c]	0.5
Overall adherence (%) [d]	91
Serum drug levels (%) [e]	
Low	40
In range	45
High/alert	15

[a] includes only medications tested in the assay; [b] the number of detected and prescribed (DAP) medications; [c] the number of detected non-prescribed (DNP) medications; [d] percent of prescribed medications that were detected, excluding drugs with half-life ≤ 4 hours (Methods); [e] for medications detected quantitively and having half-life > 4 hours, the percentage that were below, within or above the published reference ranges for each medication. De-identified patient-level results are provided in Table S2.

The same 59 medications were tested in each patient regardless of the EHR medication list. Aripiprazole was the most frequently prescribed psychiatric medication, being prescribed and detected 22 times, whereas acetaminophen was the most frequently detected medication, being detected 30 times (Table 2). Acetaminophen, omeprazole and other over-the-counter (OTC) medications were typically detected at rates higher than prescribed. When these molecules were excluded from analysis, 29 patients (25%) had medications detected but not listed in the EHR. When prescribed, OTC medications were infrequently detected, possibly because the prescribing physician issued verbal PRN instructions which would not be reflected in the EHR. Hydrocodone and oxycodone were each detected without prescription in only one patient (Table S1), and non-prescribed stimulant usage was below what we have seen in other cohorts (Table 2). These results suggest that highly-adherent patients consenting to drug testing are unlikely to be abusing prescription medications.

Table 2. Selected panel medications, prescription and detection rates and blood levels in psychiatry patients

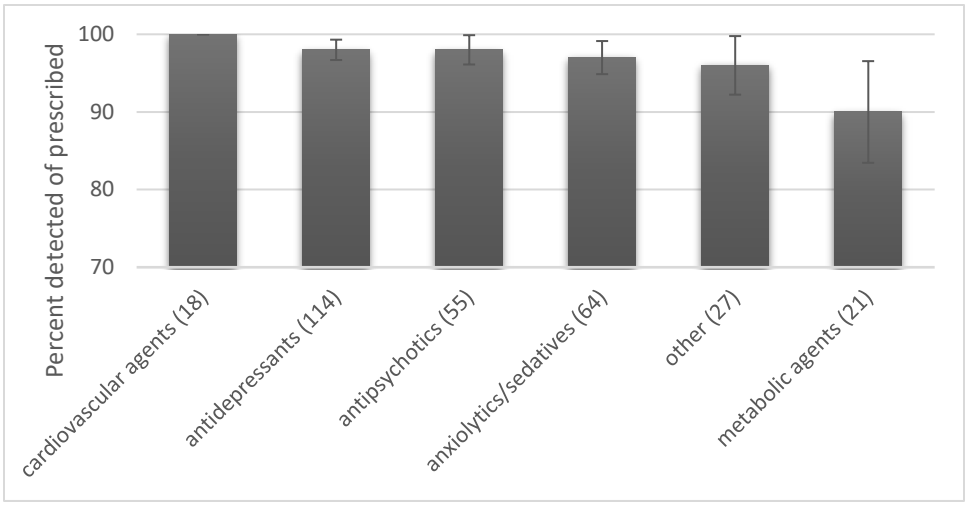
Drug[a]	half-life (hours)	Total prescribed[b]	Total detected	% detected of prescribed[b]	% not in EHR of detected[c]	% in range[d]
antidepressants						
citalopram	33	14	23	100	39	43
duloxetine	14	15	17	100	12	53
fluoxetine	120	13	13	100	0	77
mirtazapine	30	5	5	100	0	20
paroxetine	28	7	7	100	0	57
sertraline	23	12	10	83	0	100
trazodone	7.5	21	21	100	0	5
venlafaxine	5	20	20	100	0	30
antipsychotics						
aripiprazole	70	22	22	100	0	36
lurasidone	18	5	5	100	0	40
quetiapine	7	13	13	100	0	31
ziprasidone	6	10	9	90	0	44
anxiolytics/sedatives						
alprazolam	13.5	21	21	95	5	76
clonazepam	40	14	13	93	0	77
diazepam	36	5	5	100	0	N/A
hydroxyzine	13.5	6	7	100	14	0
lorazepam	14	15	15	100	0	0
anticonvulsants						
gabapentin	6	21	9	43	0	N/A
CNS stimulants						
amphetamine	6	12	6	33	33	83
methylphenidate	2	9	8	89	0	0
analgesics						
acetaminophen	2	20	30	85	43	17
ibuprofen	2	9	11	78	36	33
cardiovascular agents						
amlodipine	42	8	8	100	0	75
hydrochlorothiazide	11	14	16	100	13	63
metoprolol	5	10	11	100	9	27
metabolic agents						
atorvastatin	19.5	21	22	91	14	41
simvastatin	2.5	17	16	88	6	6
other						
bupropion	11	27	26	96	0	69
omeprazole	1	22	23	86	17	78

[a] Results for 30 additional medications with fewer than five non-PRN prescriptions and five detections provided in Table S1. All individual patient-vs-medication results are provided in Table S3. [b] Only non-PRN prescriptions; [c] EHR = "electronic health record"; [d] Percent of drug

concentrations within the therapeutic range; where four or fewer quantitative detections were obtained, 'N/A' is shown

Medications were grouped by class, separating psychotropic and central nervous system acting agents from cardiovascular, metabolic, and other agents. Adherence, as measured by the number of medications detected empirically relative to patient medical records, was greater than 97% for psychotropic medications, and only slightly less for the non-psychotropic medications assayed (Figure 1A). There are few studies comparing adherence across chronic medication classes, and none comparing psychotropic medications to other medication classes[27]. Many factors are known to contribute to medication adherence, including cost, side effect profiles, the number of concomitantly prescribed medications, and real-world medication effectiveness[28-32]. Because adherence was similar between medication classes, patients did not discriminate between psychotropic medications, where therapeutic benefits can be 'felt', and medications used to treat metabolic disease, where the treatment effect is silent. When analyzed by indication, more than 10% of detected metabolic agents and antidepressants were not listed in the EHR (Figure 1B). Collectively, prospectively enrolled psychiatry patients had more medications detected as prescribed and fewer detected medications not listed in the EHR compared to other cohorts studied[20], indicating that the medication reconciliation process produced the intended cohort bias necessary to assess medication ranges in patients who took their medications largely as prescribed.

A



B

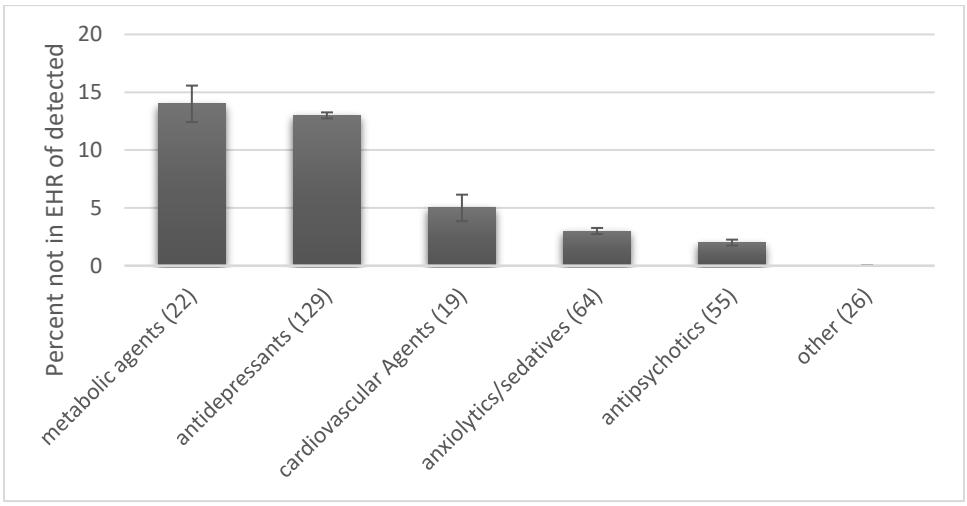


Figure 1. Medication detection relative to prescriptions in psychiatry patients. A) Percentage of prescribed medications detected B) Percentage of detected medications not listed in electronic health record (EHR). Values in parentheses denote the total number of prescriptions (A) or detections (B); error bars were calculated from Bernoulli trials.

Even though the prospective enrollment and EHR reconciliation at the time of entry produced a patient cohort that was highly adherent to psychiatry medications, 55% of medication levels remained outside the target therapeutic ranges (Table 1). As can be seen in Figure 2, 40% of detected medications were below the reference range, 45% were within the reference range, 12%

were above the reference range and 3% of detected medications were above published alert levels, where clinical evidence of adverse events have been reported. This can have a significant clinical impact, because medication concentrations above the therapeutic reference range provide no additional therapeutic benefit and may place the patient at risk for adverse events, and concentrations below have not demonstrated therapeutic benefit. Clearly, real-world variability in medication exposure is extensive, even in patients that take their medications as prescribed, and this variability is seen across all medication classes. Reasons for medication blood concentrations above or below the therapeutic reference range when taken at the proper dose and dosage interval include variation in absorption, metabolism, distribution or excretion. These factors can be influenced by genetics, drug interactions, food/nutraceutical effects, and many other intrinsic and extrinsic factors, but the relative contributions of each have not been studied in polypharmacy patients. In addition, reference ranges themselves not derived in real-world patient settings may be inaccurate. Data for some reference ranges have extensive research in non-clinical trial settings[15], whereas for other medications the data is less convincing[33]. Most medications in the current assay panel reach steady state blood levels, and therefore the lower threshold represents the lowest expected concentration achieved under chronic administration.

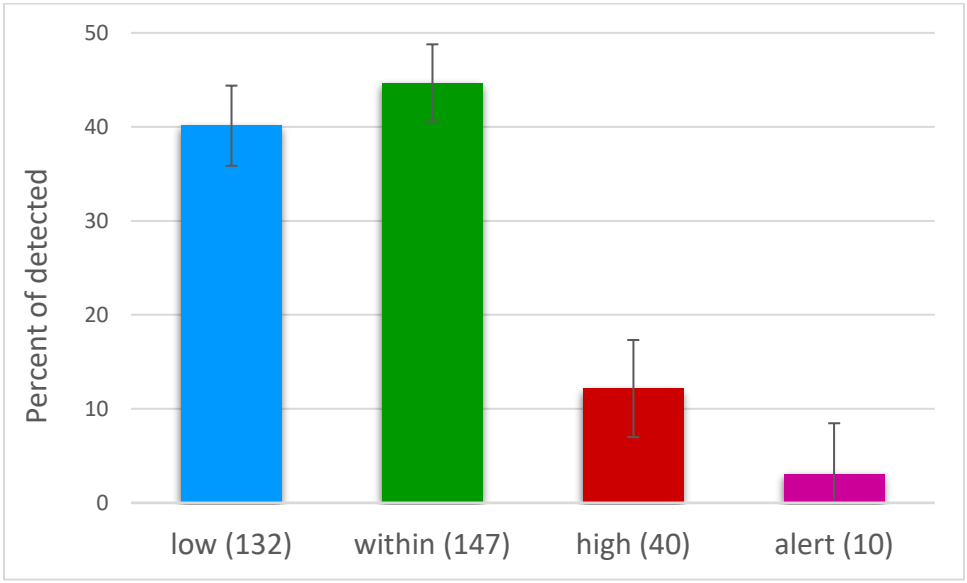


Figure 2. Detected medication concentrations relative to therapeutic reference range in psychiatry patients. Percent of medications detected that were below, within, above, or above alert levels. Summary data include all quantitatively detected medications relative to the published therapeutic reference ranges for each individual medication. Values in parentheses denote the number of detections; error bars were calculated from Bernoulli trials.

Treatment resistance and intolerance to medications is common in psychiatry, but medication exposure relative to treatment outcomes has been minimally explored. We compared exposure of each detected psychotropic medication relative to published reference ranges where patient-reported ingestion occurred less than 10 hours before blood collection (Figure 3). In this analysis, each antidepressant and antipsychotic in the test panel had at least one out-of-range medication for at least one patient. The only exception to this trend was sertraline, which was within the published reference range for all ten patients tested. Overall, 46% of psychotropic medications measured were within the therapeutic reference range, 44% were below, and 10% above.

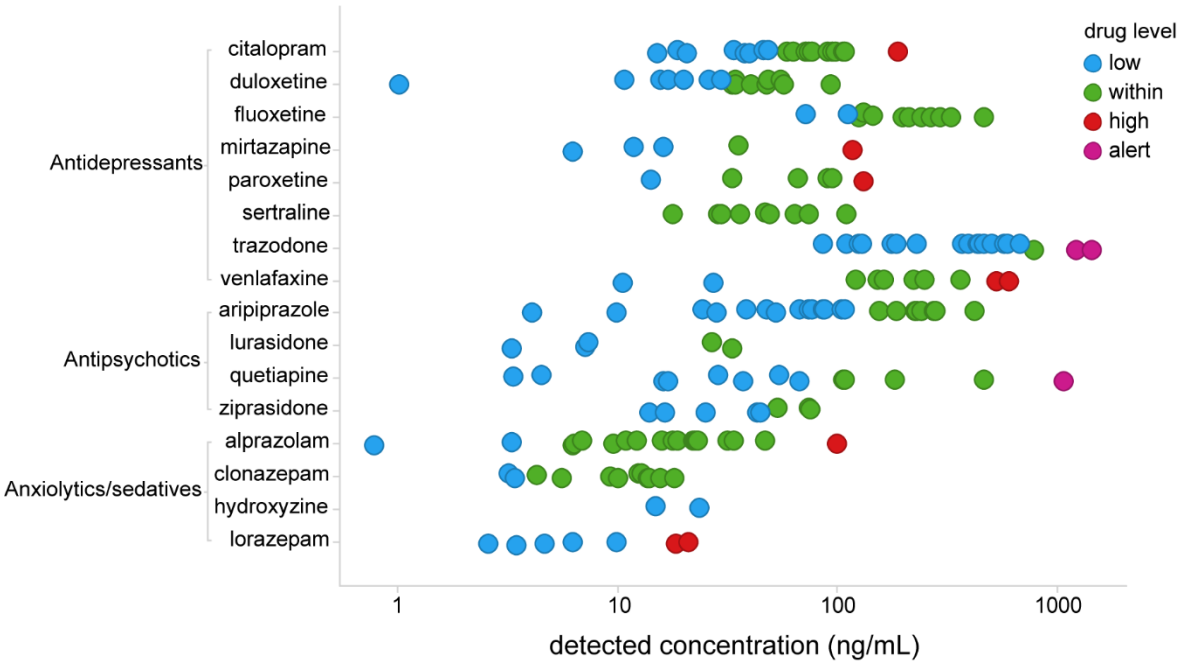


Figure 3. Single-point psychotropic medication exposure in psychiatry patients. The detected concentrations of medications in individual patients are shown for antidepressants, antipsychotics and anxiolytics detected quantitatively in 5 or more patients. Concentrations are shown on a log scale; points are jittered on the ordinate for improved clarity. Colors indicate levels vs. published therapeutic ranges. Excluded from the analysis were concentrations above the high/alert thresholds when patient-reported ingestion occurred less than 10 hours prior to blood collection, and medications below the low threshold when prescribed PRN ("as needed").

Co-morbid, polypharmacy patients have complex dosing regimens, making it impossible to obtain trough-level measurements for each of the simultaneous medications measured using the current diagnostic approach and study design. Therapeutic reference ranges are usually determined at a trough level to avoid artificially high or imprecise measured concentrations associated with peak exposure shortly after ingestion. To address this, we obtained self-reported time of dosing for each medication in the psychiatry patient EHR medication list, which allowed us to the determine the

proportion of medications below trough levels, and potentially indicative of treatment resistance. Treatment resistant disease can be defined as the failure to respond to repeated courses of medication therapy, and in the case of depression and schizophrenia can have complex underlying neurobiological and structural hypotheses[23, 25, 34]. Recent work demonstrates that over one third of treatment-resistant patients have sub-therapeutic antipsychotic levels, indicating that under-treatment may be the source of resistance in many instances[26]. Our studies indicate that patients treated with antipsychotic medications frequently experienced sub-therapeutic blood concentrations, even when following prescribed dosing regimens.

The 2017 TRRIP Working Group has created consensus guidelines addressing treatment resistance in psychosis that encourages measuring trough antipsychotic medication levels to encourage using adherence as a criterion for assessing treatment resistant schizophrenia[24]. These are the first guidelines that incorporate drug level measures as treatment-resistance criteria, and the working group noted that measures of adherence were lacking in 95% of clinical trials used in their assessment, substantiating that drug therapy is an underappreciated factor. Our data suggest that monitoring medication levels will add value beyond empiric adherence detection, as trough levels below the lower therapeutic reference range could be a factor underlying sub-therapeutic response. These findings suggest that other behavioral factors (smoking), biological factors (genetic drug metabolism status), or treatment factors (drug-drug interactions) can contribute to sub-therapeutic medication levels. More than one-third of patients taking a psychotropic medication in this study took at least one other psychotropic medication, creating ample potential for pharmacodynamic and pharmacokinetic drug interactions. In fact, there were 392 predicted moderate and major pairwise drug interactions in this 115 patient cohort using standard interaction-checking software, producing an average of 3.4 predicted interactions per patient. Current staging models for treatment resistant depression take into account patient responses to antidepressant dosing, but not exposure, therefore, therapeutic drug monitoring should be considered in treatment-resistant disease[25] .

In sum, the current study is the first to empirically assess and demonstrate that patients adhere to psychotropic and non-psychotropic medications at similar rates. Further, psychotropic medications are often out of the therapeutic range, exhibiting blood concentrations below therapeutic reference range at a ratio of 4:1 relative to being above the therapeutic reference range. These data were obtained in highly compliant, co-morbid patients, removing important behavioral factors known to drive erratic medication exposure. With these factors minimized, the healthcare provider must accept non-behavioral components as important to achieve the goals of precision medicine, and the need for exposure determination for all medications in a patient treatment regimen.

Methods

Clinical samples

The current study was conducted at the Cleveland Clinic, Cleveland, OH. Trial design was approved by the Cleveland Clinic Institutional Review Board. Patient enrollment, sample acquisition, and data collection were performed by Cleveland Clinic personnel. Quantitative sample analysis was performed by Sano Informed Prescribing, Inc., Franklin, TN.

Patients were identified by searching the Cleveland Clinic central electronic health record database for patients entering the Cleveland Clinic Department of Psychiatry and Psychology with at least one psychotropic and five total prescribed medications, two of which were represented in the test panel. Psychiatry staff were required to approve patients prior to the consenting process. Out of 140 patients approached for the study, 115 were enrolled. Reasons for declining to participate in the study included lack of time to remain after scheduled appointment, fear or unwillingness to have blood drawn, disinterest in clinical research, or too anxious to participate in this research study.

As part of the enrollment process, an interview was performed to reconcile the EHR medication list by confirming current doses of medications listed in the EHR and remove medications that were no longer being taken by the patient. The time of the last dose for each medication was also collected during this interview.

Sample collection

Samples were collected in red top gel barrier-free phlebotomy tubes and processed within 4 hours of collection. Resulting serum was frozen at -70 °C until shipment on dry ice to Sano Informed Prescribing, Inc. for analysis. The key linking study-specific identifiers to EHR information was maintained by study personnel at the Cleveland Clinic and not shared with laboratory or analysis personnel. Laboratory personnel were blinded to study participants' records, including the EHR medication list, during the measurement phase of the study.

LC/MS/MS analysis

Sample analysis was executed under the guidelines set forth by the CAP and standard operating procedures commensurate with CLIA-registered operations. Samples were thawed, mixed, and transferred to 96-well plates for processing. Internal standard working solution was added and protein precipitation was performed using Phenomenex Impact Protein Precipitation Plates. Eluate was transferred to a new plate and dried under Nitrogen prior to reconstitution for LC/MS/MS analysis. Reconstituted samples were processed using a Shimadzu Nexera X2 liquid chromatography system (Columbia, MD) fitted with a Phenomenex 2.1 x 50 mm, 1.7um C18 column (Torrence, CA). Sample analysis was performed on a Sciex 5500 Q-Trap Mass Spectrometer (Framingham, MA) with TurboV ion source. Data collection was performed with Sciex Analyst software, version 1.6.2, and data analysis was performed using Indigo BioAutomation Ascent software (Indianapolis, IN).

Optimal grade methanol and acetonitrile were obtained from Fisher Scientific (Waltham, MA). Formic acid, ammonium acetate, ammonium formate, and water were LC/MS grade and obtained from Sigma-Aldrich (St. Louis, MO). Dimethylsulfoxide was obtained from Sigma-Aldrich. Ammonium hydroxide was obtained from Thermo Fisher Scientific. Drug naïve human serum used in validation studies was obtained from Bioreclamation IVT (Westbury, NY). All analytical standards were obtained at the highest purity available. Stock solutions were prepared individually in DMSO, water, methanol, or acetonitrile, then combined. Standard Curve and Quality Control samples were prepared in drug naïve human serum. Assay linearity, precision, accuracy, and detection were assessed by adding various amounts of each test drug to human serum. Each of the analytes assayed passed strict analytical validation criteria. In an earlier assay versions, bupropion was shown to exert plasma instability, therefore, the metabolite hydroxybupropion was used as a surrogate measure of

parent as previously demonstrated[35]. The final test panel detected the presence of 84 unique analytes, corresponding to 59 parent drugs (Table S1).

Quantitative Medication Reporting

After measurement, deidentified medication lists from each patient's EHR was compared to LC/MS/MS data. Reference ranges for each of the 59 parent drugs were obtained using triaged data sources as indicated in Table S1. The primary information source was the AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry, which provides an evidence-based therapeutic reference ranges for 128 marketed psychiatric medications. If the medication was not listed in this primary source, secondary sources derived from primary literature were utilized. Finally, if no literature values could be obtained, drug label information was utilized[33, 36-40]. Medications were mapped to drug classes according to the NHANES resource (https://wwwn.cdc.gov/nchs/nhanes/1999-2000/RXQ_DRUG.htm; accessed 3/9/2017.

Table S1 lists the 59 medications assessed in each patient using this medication panel. Each parent medication assayed in the test panel was prescribed or detected in at least one patient, with the exceptions of amiodarone, digoxin, iloperidone, lovastatin, methamphetamine, phenytoin, risperidone, tramadol, verapamil, and warfarin. In addition, drugs which are also metabolites of other medications were detected. For example, although oxazepam was never prescribed, it was detected 7 times as a metabolic breakdown product in patients taking diazepam or temazepam. We excluded 16 drugs with half-life ≤ four hours from summary analyses in Figures 1-3 (Table S1). However, it should be noted that five such drugs were prescribed nine or more times and had detection rates ≥78% (acetaminophen, ibuprofen, methylphenidate, omeprazole, simvastatin; Table S1). Thus, LC/MS/MS detection results may provide useful data on adherence for many short half-life drugs.

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