Clinician's perspective to a personalized pharmacotherapy of patients with intellectual disabilities and autism spectrum disorder

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SUMMARY

Introduction: Biomarkers emerging from the industry-driven pharmacogenomics research have been hoped to lead to individualized medicine therapy, i.e. better efficacy and tolerability of pharmacotherapy. From a clinician's perspective, the current system for routine registration of long-term pharmacotherapeutic effects is insufficient for optimal realization of individualized treatment. It is also evident that the biomarkers cannot be translated into clinical practice without a pertinent case-by-case knowledge on drug response and adverse reactions. Consequently, a phenotype-based monitoring would be needed as a prerequisite for achieving personalized medicine therapy especially when treating intellectually disabled patients with neuropsychiatric co-morbidities.

Problem description: In order to benefit the available biomarkers in the care of patients on long-term medication, we need easily obtainable patient-specific information of efficacy and safety of drug therapy. The possibilities to create such data for a later quick read from the current medical records are lacking. Therefore, there is an emergent need for a simple clinical tool for the systematic registration of individual pharmacotherapy, which means that the currently used flow chart should be amended with additional columns for indications, therapeutic benefits and disadvantages.

Suggested solution: The medical history collected retrospectively at Rinnekoti-Foundation during years 2010–2012 from our nine intellectually disabled patients diagnosed with autistic spectrum disorders, suggests that such tool would be both practical and useful. It is difficult to see how the pharmacogenetic and other biomarkers could be benefited fully in the routine patient care without pertinent records on individual effects of prescribed medicines. Units providing health services for intellectually disabled patients could serve as test platforms for the development of a new flow chart once there would be an expert team to collaborate with and to manage technical challenges. The suggested flow chart might help clinical decision making when managing any patient on long-term pharmacotherapy.

Keywords: autism, behavioral symptoms, epilepsy, intellectual disability, personalized pharmacotherapy

Challenges in the utilization of innovations emerging from pharmacogenomics and molecular research in clinical practice

Molecular innovations in neuroscience and advances in understanding the human genome have encouraged the pharmaceutical industry to move from concentrating on broad spectrum population therapeutics towards focusing on personalized medicine (Wong *et al.* 2011). However, due to complexity of neuropsychiatric diseases, the translation of pharmacogenomics research findings into clinical practise has been unimpressive mostly because of insufficient knowledge of how genotype correlates with phenotype (Crews *et al.* 2012, Evrard & Mbatchi 2012, Monte *et al.* 2012). From a practitioner's perspective, the lack of a pertinent clinical tool for systematic online, case-by-case registration of indication(s) as well as of desired and undesired pharmacotherapeutic effects are all significant impediments on this long road.

In most cases, the systematic follow-up of pharmacotherapy virtually ceases after approval of marketing authorization for a medicine. At present post marketing surveillance normally consists of only spontaneously reported adverse responses, i.e. it is solely the clinicians' responsibility to report and record individual adverse drug responses. Unsurprisingly, a PubMed search did not reveal any relevant studies, which would have investigated medical reports (i.e. clinician's role) in relation to records written from optimal pharmacotherapy. One cross-sectional study by de Kuijper and co-workers (2010) indicates that even the reason for writing the prescription may be missing from the intellectually disabled (ID) patients' medical records. Thus, it is clear that routine reports about individual drug responses should be more informative than what they currently are and not only because of pharmacological reasons but also because of diagnostic uncertainties.

Health management of subjects with intellectual disabilities and several co-morbidities is extremely challenging for several reasons. Firstly, both epileptic seizures and various behavioural disorders are commonly present in this patient group (Koskentausta *et al.* 2002, Kerr *et al.* 2009). Secondly, the symptoms and/or natural course of these co-morbidities may be highly variable depending on the underlying aetiology of intellectual disability and various psychosocial factors (Koskentausta *et al.* 2002, Kerr *et al.* 2009, Bjelogrlic-Laakso *et al.* 2014). Thirdly, according to a common clinical experience, the long-term medical history needed to implement the personalized medicine therapy is often either inaccessible or non-existent. Furthermore, pharmaceutical management of concomitantly occurring epileptic and psychiatric symptoms is a two-edged sword; e.g. serotonin reuptake inhibitors and neuroleptics may worsen seizure control whereas antiepileptics may be associated e.g. with cognitive impairment and behavioural adverse events (Kerr *et al.* 2011, Perucca *et al.* 2012). In addition, specific psychiatric diagnostics is extremely challenging resulting in an unfortunate fact that the off-label use of pharmaceuticals within this patient group is more a rule than an exception (Kerr *et al.* 2009, de Kuijper & Hoekstra 2017, Bjelogrlic-Laakso *et al.* 2014, 2020).

The idea for a new type of flow chart has risen from the practical need to easily obtain clinically relevant information for viewing and updating during an appointment or on routine clinical rounds. In order to test the usability as well as usefulness of this kind of a clinical tool, the medical history that was available retrospectively from the conventional medical records, was collected from intellectually disabled patients diagnosed with autistic spectrum disorder (referred to subsequently as 'autism'). All nine patients on long-term rehabilitation (during years 2010–2012) in closed autism units of Rinnekoti-Foundation were chosen for testing as they represent of the most challenging patient group concerning long-term polypharmacy. Of note, here is that due to the severity of destructive and behavioural symptoms a maximum of three or four patients can be accommodated in one unit.

Autism with an intellectual disability and other possible co-morbidities (e.g. epilepsy, psychiatric disorder) is a lifelong pervasive developmental disorder characterized by deviance in social interaction, verbal and nonverbal communication and in addition, it is frequently associated with treatment-resistant neuropsychiatric disorders (Palermo & Curatolo 2004, Kaplan & McCracken 2012, Woolfenden *et al.* 2012). The current pharmacotherapy for autism target the specific symptoms without addressing the basic underlying aetiologies, but recent advances in experimental animal models as well as increased understanding of the biochemistry and neuropathology of autism related disorders such as Fragile X syndrome will hopefully lead to novel pharmacotherapeutics (Chadman *et al.* 2012, Hampson *et al.* 2012, Pandina *et al.* 2020). However, medical management of this patient group remains a major challenge to clinicians for three major reasons. 1) At present, no evidence-

Figure 1. a) An example of desired online pharmacotherapy flow chart of a patient with intellectual disabilities and autism spectrum disorders. The information provided to the flow chart includes patient information (name, date of birth, social security number), diagnosis, medication (initiation date, dosage, indication, response and adverse reaction).

Patient								**Diagnosis**				
Date of birth, social security number												
Medicine	Dose	time 8	time 12	time 16	time 19	Initiation date	Discon-tinuation date	Indication / symptom*)	Response /Adverse reaction(s)			
									≤ 1 month **)	≤ 3 months **)	≤ 6 months **)	≥ 12 months **)

***) Indication / symptom:**
1. Self injury
2. Aggression
3. Restlessness, irritation
4. Depression / anxiety symptoms
5. Obsessive compulsive behavior
6. Hallucinations or amelioration of other symptoms
7. Other psychiatric symptom(s)
8. Generalized epilepsy
9. Focal epilepsy
10. Other epilepsies
11. Dementia / other neurol. symptoms
12. Other somatic symptoms

****) Response / Adverse reaction(s):**
++++ = full response
+++ = partial response
++ = weak response
+ = weak response, amelioration of other
0 = no response/adv.
- = mild adverse reactions
-- = significant adverse reactions

b) An attachment to the online pharmacotherapy flow chart containing a summary table of biomarkers, etiological and neurophysiologic findings and other pharmacologically relevant patient information.

Patient		**Diagnosis**
Date of birth, social security number		
Hypersensitivities		
Family history		
Etiological evaluations	**Date of evaluation**	**Major findings**
Cerebral MRI or CT		
Chromosomal examinations		
Frax-DNA-analysis		
Evaluation of urine metabolites		
EEG		
Video-EEG or other neurophysiologic examination		
Pharmacogenetic markers		
Others		
Comments (further description of study results, e.g. unexpected findings)		

Table 1. Characteristics of nine intellectually disabled patients on long-term rehabilitation in closed autism units of Rinnekoti-Foundation during years 2010–2012.

Case*	Age (yrs)	Female / Male	Number of years on medication	Past medication**	Current medication**
1	32	M	28	CBZ, mianserin, melperone, chlorprothixene, citalopram	VPA, oxybutynin, LMP, citalopram, cetirizine
2	18	M	13	-	VPA, TPM
3	64	M	50	chlorprothixene, TZ, CLB	PPZ, risperidone, OLZ, lansoprazole, propranolol
4	26	M	16	citalopram, flupenthixol, PC	CBZ, risperidone, sertraline, chlorprothixene, cetirizine, magnesium
5	23	F	21	CBZ, VPA, OXC, FLX, OLZ, risperidone, mirtazapine	QTP, lorazepam, LTG, cetirizine
6	19	M	≥ 3	OLZ, risperidone	VPA, aripiprazole, melatonin, escitalopram, oxazepam
7	15	M	9	risperidone, citalopram, CBZ, PC, CPZ, CLZ	melatonin, LMP, mesalazine, VPA, OLZ, pregabalin
8	18	M	> 6	chlorprothixene, citalopram, risperidone, LMP, oxazepam, CBZ, aripiprazole	cetirizine, LMP, lorazepam, escitalopram, QTP, risperidone
9	24	M	4	risperidone, LMP, diazepam, VPA, QTP, sertraline, ziprasidone, OLZ	VPA, aripiprazole, MEM

** Cases 1 to 5 represent patients diagnosed with Fragile-X syndrome and cases 6 to 9 autism of unknown aetiology. Additional co-morbidities include behavioural disturbances (all cases), epilepsy (cases 1, 2 & 5), essential tremor (case 3), psychosis (case 5), cerebral pseudotumor (case 5) and ulcerative colitis (case 7). Severe aggressive behaviours are ongoing in case 6.*
*** Medicines mentioned in both lists of past and current medications have been reinstated later.*

Abbreviations: Carbamazepine (CBZ), Chlorpromazine (CPZ), Clobazam (CLB), Clozapine (CLZ), Fluoxetine (FLX), Lamortigine (LTG), Levomepromazine (LMP), Memantine (MEM), Pericyanizine (PC), Perphenazine (PPZ),Olanzapine (OLZ), Oxcarbazepine (OXC),Thioridazine (TZ), Topiramate (TPM), Valproic acid (VPA), Quetiapine (QTP).

Table 2. Data collected from the conventional medical records of nine patients with intellectual disabilities, autism and other co-morbidities (see the patient characteristics from Table 1.)

	Fragile-X syndrome	Autism (aetiology unknown)
Number of cases (n)	**5**	**4**
Number of current medicines / overall number of medicines used over the life-span	case 1: 5 / 9 case 2: 2 / 2 case 3: 5 / 8 case 4: 6 / 9 case 5: 4 / 11	case 6: 5 / 7 case 7: 6 / 12 case 8: 6 / 13 case 9: 3 / 10
Number of medicines with known indication over the life span / number of overall medicines used over the life span (%)	case 1: 8 / 9 (89%) case 2: 2 / 2 (100%) case 3: 7 / 8 (88%) case 4: 9 / 9 (100%) case 5: 10 / 11 (91%)	case 6: 7 / 7 (100%) case 7: 11 / 12 (92%) case 8: 12 / 13 (92%) case 9: 10 / 10 (100%)
Number of medicines with recorded response over the life span / number of overall medicines used over the life span (%)	case 1: 1 / 9 (19%) case 2: 1 / 2 (50%) case 3: 4 / 8 (50%) case 4: 0 / 9 (0%) case 5: 8 / 11 (81%)	case 6: 6 / 7 (86%) case 7: 7 / 12 (58%) case 8: 11 / 13 (85%) case 9: 10 / 10 (100%)

based effective pharmacotherapeutic options are available for treating the core deficits of autism (Kaplan & McCracken 2012, Pandina *et al.* 2020). 2) Differential diagnostics between autism and neuropsychiatric disorders is difficult and 3) The overall risk/benefit profiles of the available medicines for symptomatic treatment remain questionable (Hurwitz *et al.* 2012, Hirsch & Pringsheim 2016, Bjelogrlic-Laakso *et al.* 2020).

Practical tool needed for optimizing both the recording of pharmacotherapy and clinical decision making

In order to tackle the inevitable everyday pharmacotherapeutic challenges in clinical realm, a conventional timeline passing pharmacotherapy flow chart could be developed for the systematic registration of individual drug responses in order to complement the current attempts towards achieving more personalized medicine therapy. This means that the current flow chart (incl. names, dosages and dates) would be amended with extra columns for indication as well as response and adverse events as shown in **Figure 1**.

To test the applicability of the suggested flow chart, we discussed in the multidisciplinary team (incl. a neurologist (an author), a psychiatrist, a psychologist) the current medications and their efficacies with nurses on weekly clinical rounds, read through the medical records of each patient, and collected all the relevant data to the table shown in **Figure 1a** and to **Tables 1 and 2** by writing down by hand. Characteristics of the selected nine patients are described in **Table 1**. **Table 2** shows the individually collected information according to the number of past and current medicines, indications and drug responses.

As anticipated, deficiencies were found in the recording of individual medicine therapy as shown in **Table 2**. The reason for issuing the prescription was found in our randomly chosen nine cases for almost every medicine used either currently or in the past (89–100%). This was a slightly better result than that reported in a cross-sectional study conducted in the Netherlands with a larger population (n = 2373) demonstrating that in 81.5% of cases the indication was available (de Kuijper *et al.* 2010). Individual drug responses were not studied by de Kuijper and co-work-

ers (2010). In this survey those were found from the medical reports randomly: Only in one case (no 9) drug responses were recorded for all used medicines. In the rest of the eight cases, an individual drug response was found from the medical reports at some time point only or in one case (no 4) not at all.

Furthermore, in order to obtain all the necessary information available for a quick review in clinical rounds, a summary table including information on aetiologies, most significant examination findings and potential biomarkers would be helpful as a fixed attachment to the revised flow chart. An example of such flow chart is presented in **Figure 1b**.

Current challenges

The current system for routine registration of indications and long-term pharmacotherapeutic effects is inappropriate and/or too arbitrary for optimal realization of individualized treatment as indicated in this survey and as shown also by the others (de Kuijper *et al.* 2010). This basic defect should be considered while translating the results of pharmacogenomic analysis into successful clinical practice. The pharmacotherapeutic challenges in medical recording described in this commentary do reflect our own experience with autistic ID patients, but they are most likely applicable also to the management of other disorders requiring long-term medication.

Phenotype-based monitoring should be encouraged for all patients on long-term pharmacotherapy as a prerequisite for achieving personalized medicine therapy. One way to achieve this goal might be to amend the currently used flow charts to include extra columns for indications, therapeutic benefits and disadvantages as suggested in this commentary. In an ideal case, the revised online flow chart would be part of an electronic patient record to make it applicable for everyday use in the clinical routine.

Experienced and expected benefits of the improved medical records

In the clinic that provides medical services for persons with intellectual disabilities, the new pharmacotherapy flow chart was commonly felt to improve the communication between clinicians and nurses as discussed in team meetings. This is of crucial importance, since intellectually disabled patients often have a limited capability for verbal self-expression. Consequently, the clinician may enjoy a greater possibility of making the most advantageous decision when he/she has to devise the optimal pharmacotherapy on a case-by-case basis. Additionally, the presented approach was considered to improve medical standards within the units by increasing the general knowledge in clinical pharmacology and thus, by helping to achieve as optimal outcome as possible.

An improved medical recording of individual pharmacotherapy would most likely increase the rational use of pharmaceuticals by encouraging the readiness of practitioners to register the desired and undesired effects of any new medication. It is noteworthy that symptoms may improve occasionally also because of some non-pharmacological interventions or concomitant, unexpected events in the patient's environment. Thus, it is crucial to acknowledge all confounding factors when evaluating pharmacological effects on individual basis. This requires a good and reliable information (and, thus, understanding) of the medical history of a patient, which may not always be currently available resulting in unfavorable outcome. Putting more emphasis on medical recording may have multifaceted positive consequences at least to the daily lives of intellectually disabled patients most of whom are dependent on the others' assistance throughout their lives.

Interestingly, our data revealed one unexpected drug response. In case 2, the aggressive behaviour had been successfully treated with topiramate (50 mg x 2 per day), an antiepileptic, which is known to exert a variety of neuropsychiatric adverse events (Besag 2001, Canitano 2005). This example highlights the importance of 'phenotype-based' personalized medicine therapy; sometimes treatment resistant symptoms may be alleviated by unorthodox therapy. Occasionally these kind of findings can lead even to new significant scientific discoveries. It may not necessarily be too speculative to claim that the improved medical recording could increase our overall medical knowledge in many unexpected ways.

TIIVISTELMÄ

Kliinikon näkökulma autismikirjon häiriöistä kärsivien kehitysvammaisten potilaiden yksilölliseen lääkehoitoon

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Johdanto: Teollisuusvetoisesta farmakogenomiikan tutkimuksesta tulevien biomarkkereiden on toivottu johtavan yksilöityyn eli tehokkaampaan ja paremmin siedettyyn lääkehoitoon. Kliinikon näkökulmasta nykyinen pitkäaikaisen lääkehoidon rutiinirekisteröintijärjestelmä on riittämätön yksilöllisen lääkehoidon optimaaliseksi toteutumiseksi. On myös selvää, että biomarkkereita ei voida viedä kliiniseen käytäntöön ilman asianmukaista, tapauskohtaista tietoa lääkevasteista ja haittavaikutuksista. Täten fenotyyppiin perustuva seuranta olisi välttämätön edellytys yksilölliseen lääkehoitoon asetettujen päämäärien saavuttamiseksi erityisesti hoidettaessa kehitysvammaisia potilaita, joilla on neuropsykiatrisia liitännäissairauksia.

Ongelman kuvaus: Jotta käytettävissä olevia biomarkkereita voidaan hyödyntää pitkäaikaista lääkehoitoa käyttävien potilaiden hoidossa, tarvitsemme helposti saatavilla olevaa potilaskohtaista tietoa lääkehoidon tehokkuudesta ja turvallisuudesta. Mahdollisuudet tällaisen tiedon luomiseksi niin, että ne olisivat myöhemmin nopeasti luettavissa nykyisistä sairauskertomuksista, puuttuvat. Täten yksilöllisen lääkehoidon seurantaan tarvitaan yksinkertainen työkalu, mikä tarkoittaa, että nykyiseen lääkekorttiin pitäisi lisätä sarakkeet indikaatioiden, terapeuttisten hyötyjen ja haittojen rekisteröimiseksi.

Ehdotettu ratkaisu: Yhdeksältä autismikirjon häiriön diagnoosin saaneelta, älyllisesti kehitysvammaiselta potilaaltamme Rinnekoti-Säätiössä vuosien 2010–2012 välillä retrospektiivisesti kerätyt sairaushistoriat viittaavat siihen, että tällainen työkalu olisi sekä käytännöllinen että hyödyllinen. On vaikea nähdä, kuinka farmakogeneettisiä ja muita biomarkkereita voisi hyödyntää täysimääräisesti rutiininomaisessa potilaan hoidossa ilman asianmukaisia kirjauksia määrättyjen lääkkeiden yksilöllisistä vaikutuksista. Yksiköt, jotka tarjoavat terveydenhuollon palveluita kehitysvammaisille potilaille, voisivat toimia testialustoina uutta lääkekorttia kehitettäessä, kunhan sinne saataisiin teknisiä haasteita hallitseva asiantuntijaryhmä mukaan yhteistyöhön. Ehdotetun kaltainen vuokaavio voisi helpottaa kliinistä päätöksen tekoa hoidettaessa kaikkia pitkäaikaislääkehoidossa olevia potilaita.

Avainsanat: autismi, käytösoireet, epilepsia, kehitysvammaisuus, yksilöllinen lääkehoito

CONFLICTS OF INTEREST

No conflicts of interest.

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