Submission to Public Accounts Committee

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Patient experiences. It is distressing to listen to a patient whose experiences with their illness and its treatment have been undervalued or worse, ignored. *Some years ago, a gentleman in his 60s recounted his deep despair and distress with the discounting of his recurrent severe reaction to morphine injections. Every time he presented to an Emergency Department, his story was not believed and morphine administered with, to him, predictable and devastating results. He was crying as he spoke to the community consultation I was part of.* Too often patients/consumers have similar stories but the stories of people with mental illness are even more likely to be dismissed. The Medication & Mental Illness: Perspectives report of the Mental Health Commission of NSW 2016 documents this starkly. I'll make the case that such experiences need to be pursued and investigated in order to learn for the well being of that patient but also future patients.

Two specific issues that I have been asked to address are 1*) pharmacogenetics as a major contributor to adverse outcomes* and 2) *adverse events and reactions as a significant impact upon patients and the health system as a whole, with implications for health care resources and costs*.

Medication Errors. Medication errors (errors in the prescribing, supply, preparation, administration, or monitoring of a medication) are the single most preventable cause of patient harm. In 2010 in the USA 1.5 million people were harmed costing US$ 3.5 billion *per annum.*(1) This has been described as a "Modern Epidemic". It is a global problem to the extent that **WHO announced 'Medication Without Harm' in 2017** as the next global patient safety challenge.(2) The world wastes an 'eye-watering' $42 billion annually on medication errors, approaching 1% of global health expenditure.

Every day 7 out of 100 patients admitted to our hospitals has an adverse reaction to medicines and for 80% of these, this was the reason for the admission. Medication related hospital admissions in Australia are estimated to be around 6% in Emergency Departments, about 13% for Medical admissions, and from 15-nearly 40% for admissions to Geriatric Wards. Overall medication related admissions are 2-3%. (3, 4)

What medications is the patient actually taking? *It is disturbing when a patient tells me that her GP disputes that the dose of her antihypertensive is 0.5 mg but actually 4 mg, and continues to write the prescription accordingly. This patient has a specialist cardiologist, endocrinologist, gastroenterologist and rheumatologist (me) who all prescribe her medicines for her multiple conditions. Not surprisingly, she has had multiple falls.* Knowing what a patient's medicines are and what they are actually taking is critical when there are multiple conditions co-existing, multiple medications and multiple doctors involved. ***These problems are more common when such a patient has a concomitant***

mental illness and usually additional medicines for that condition. This is one of the reasons for a national effort to focus on this problem named Reducing Adverse Medication Events in Mental Health (RAMEMH) working party that I am a member of that advises State and Federal Health agencies. Hazardous times for the patient with respect to their medications are transfers between hospital, residential aged care facility, hospital, and outpatients department.

Medication Reconciliation Reviewing a patient's actual medicines taken with the patient is a revealing and a valuable exercise – why? This is sometimes called 'Medication Reconciliation' and much attention has been given to implementing this effectively. (5, 6) Not uncommonly it reveals the reason for the new symptoms such as dizziness on standing, falls, fracture hip, confusion, drowsiness, constipation, urinary retention etc. *For example, the discovery that a person is taking two 'brands' of the same popular antidepressant, sertraline, namely Setrona and Sertra 50, that have been prescribed is the probable reason for the excessive sedation and falls and also a risk for the dangerous 'serotonin syndrome'.* The rationale for psychoactive medications a patient is taking is often challenging e.g. two or more benzodiazepines at once, or prescription of antipsychotic medicines without a history of psychosis.

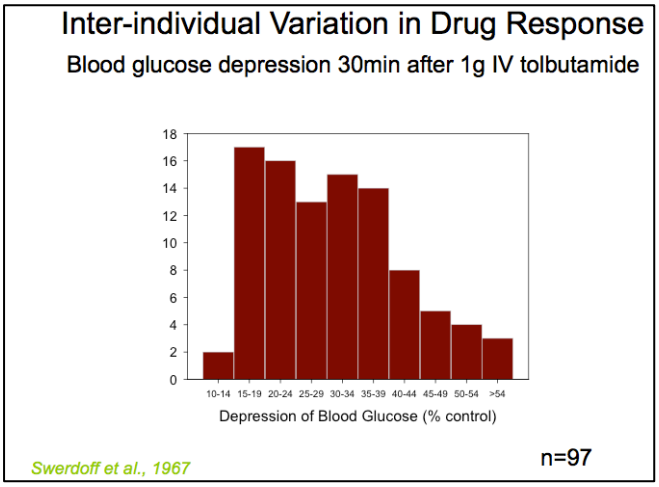
Additional hazards from medication for people with mental illness. Patients with mental illness have predictably and significantly lower life expectancy due to their co-morbidities such as type II diabetes and the increased cardiovascular risks thereby associated. (7) Actually some of this comorbidity is related to the adverse effect of antipsychotic and antidepressant medicines. (8) Simply the

burden of the number of medicines a patient is taking, that is ***polypharmacy,*** and uncertainties about 'who' if anyone is aware of all of these, their rationale, and the possibilities of interactions amongst them is unfortunately common.(9) This opens the possibility of a ***'prescribing cascade'*** where an adverse reaction is unrecognized as such and leads onto a new prescription to treat the adverse reaction to the first medicine. *For example, an elderly person is treated with a cholinesterase inhibitor for their dementia and develops incontinence. Unrecognised as an adverse drug reaction, an anticholinergic drug is prescribed that worsens the patient's mental state, causes constipation and risks an acute rise in intraocular pressure from the patient's glaucoma.(10)* Then there are important interactions with smoking, alcohol and marijuana, all more commonly encountered and experienced by persons with mental illness.

Quality Use of Medicines provides the framework for action. Before addressing the matter of pharmacogenetics as a major contributor to adverse outcomes I commend to the Committee the Quality Use of Medicines or QUM component that is the centrepiece of the National Medicines Policy 1988 as a framework for understanding and taking action on the matter of adverse outcomes associated with the pharmacological management of mental illness. Importantly this policy was consumer driven from the outset related to the same concerns being investigated by this Committee today, that is overuse, underuse, inappropriate use and adverse consequences of medicines use. The 'core', as I teach my students seems disarmingly simple***: 1) Selecting management options wisely 2) Choosing suitable medicines if a medicine is considered necessary 3) Using medicines safely and effectively.*** I call this the QUM filter and

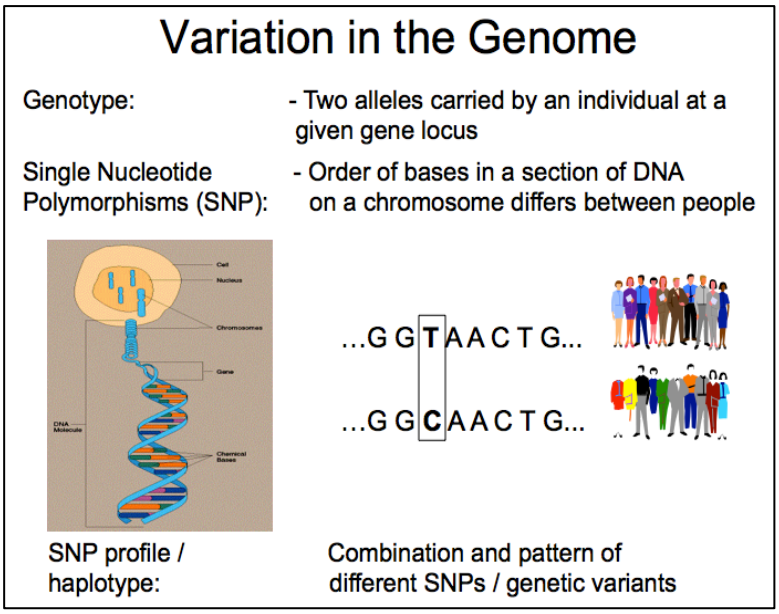
challenge them to see if any patient they are 'clerking' survives this test. In Australia, usefully, the term 'medicines' as used in the policy incorporates not only prescription medicines but also 'over the counter' as well as 'complementary' medicines, the latter not being the case in USA and New Zealand, to their detriment. *For example, St Johns wort, commonly used in depression is an important cause of drug interactions as well as a potential contributor to the 'serotonin syndrome'.(11, 12)* The policy is based upon 'partnerships' involving all groups who influence QUM, across all settings and is reliant on 'behaviour' change.

Drug Therapy is best 'individualised'. A key element pertinent to the impact of pharmacogenetics on adverse outcomes is point 3 of the 'QUM filter' namely ***Using medicines safely and effectively.*** A key tenant of therapeutics captured in this point is that more often than not, ***doses need to be individualised.*** Thus, the person's age, sex, weight, organ functions, ethnicity, concomitant medicines and alcohol and tobacco use may all need to be considered. The concentrations of medicines in blood, which we measure for critical drugs such as immune modulators for transplantation, antibiotics, antiepileptics, and some antipsychotics etc varies **very** widely between people. ***This is important because the amount of effect, both good and bad, relates to the concentration of medicine at its site of action in the body.***

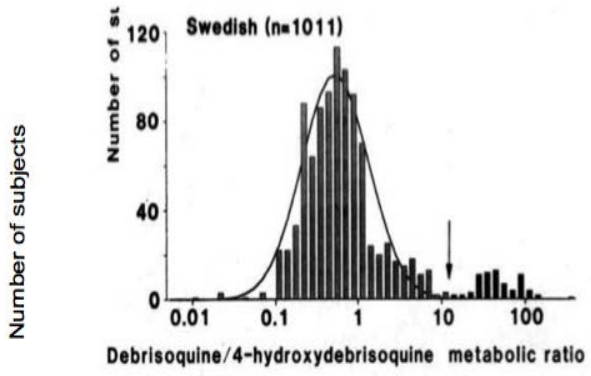


Pharmacogenetics has emerged in the 1970s as an important modulator of outcomes in individuals and this applies particularly to medicines used to treat Mental Illness. *The first example that impacted me was in fact in the 1970s where I was involved in a clinical trial of an antidepressant. The subjects were normal volunteers, in fact medical students and each was given a single, low dose and bloods collected throughout the day to measure the concentration of the drug. One of the eight or so volunteers promptly slept and couldn't be easily roused at the end of the day when his mother arrived to pick him up! It turned out he had a mutation in the gene that was responsible for synthesis of an enzyme/protein critical for the metabolism and detoxification of the antidepressant. This enzyme was cytochrome P450 2D6, and that student was in high demand for further clinical research studies.*

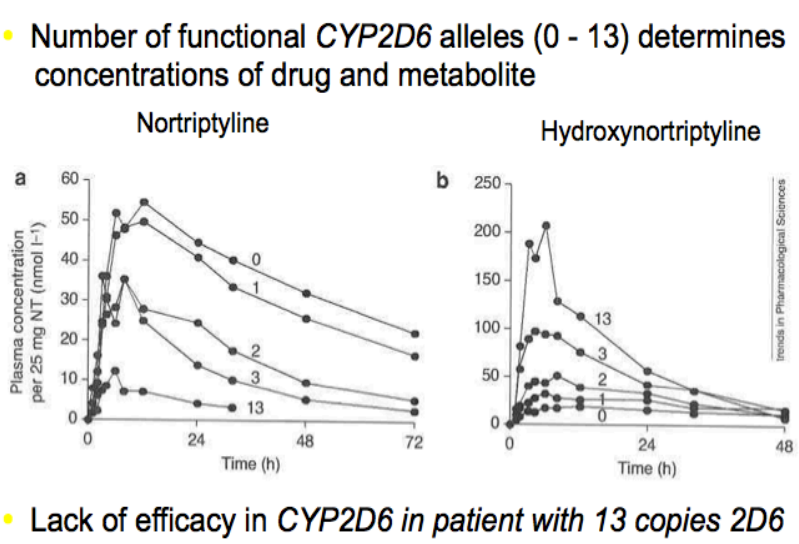
Pharmacogenetic Mechanisms. Pharmacogenetics can affect the outcomes from administration of drug in two ways: its disposition in the body ***(Pharmacokinetics (PK) or "what the body does to the drug")*** or its effect on the body ***(Pharmacodynamics (PD) or "what the drug does to the body").***



Variations in our genomes leads to variation in protein structures, and proteins carry out critical functions such as metabolising and transporting medicines across barrier membranes. The cytochrome P450 enzyme system is the primary pathway for metabolising medicines and ***there are 4 of many that are subject to 'polymorphisms'***, such that genetic variation can lead to very large effects on the metabolism of drugs reliant on that enzyme. These enzymes are Cytochrome P450 (CYP) 2D6, 2C9, 2C19 and 3A5 and they



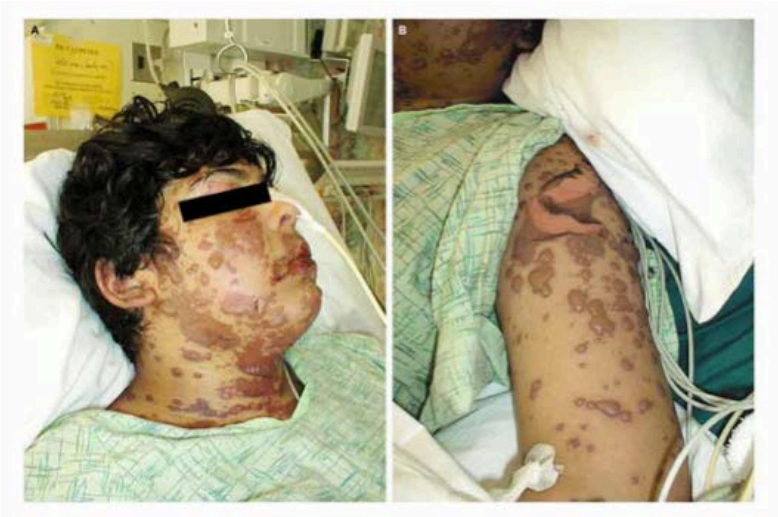
are responsible for metabolizing a very large proportion of all the medicines we prescribe.(13) These variations that can affect the function of the proteins that are formed. Important enzymes for medicines prescribed in mental illness like 2D6 and 2C19 can have no function so that the drug is much more slowly removed leading to possibly dangerous adverse effects. In Caucasian populations about 8% of people do not have functional 2D6 and therefore will likely be over sedated, perhaps dangerously so with usual doses. On the other hand there can be variants such that the enzyme is more functional or there are multiple copies of the gene for 2D6 meaning that there is much more enzyme to metabolise the drug. In this situation the drug is removed from the body very quickly and there is no or little effect **(Figure)**. *I had a patient referred who had inflammatory bowel disease and reacted very badly to Imuran (azathioprine) due to a genetic deficiency in an enzyme that we check before prescribing Imuran (TPMT). She was commenced on a series of antidepressants, including nortriptyline, all metabolized by 2D6. She didn't improve. The diagnosis was doubted increasing her distress. She was a fast metabolizer with multiple copies of 2D6 and could not achieve effective drug concentrations. An antidepressant not metabolized by 2D6 was prescribed.*



Type B (bizzare) Adverse Drug Reactions. These serious adverse reactions used to be called idiosyncratic as we were uncertain about the mechanisms.

Features	*Type A*	*Type B*
Pharmacology	Augmented	Bizarre
Predictability	Yes	No
Dose-dependence	Yes	Generally No
Morbidity	High	High
Mortality	Low	High
Frequency	Common	Uncommon
First Detection	Phase I-III	Phase IV, sometimes III
Animal Models?	Usually	None known

(Figure) We now know that some are strongly genetically determined. This applies to carbamazepine (Tegretol), a drug used for epilepsy, but also for bipolar mood disorder. Thus, the feared Stevens Johnson Syndrome pictured here **(Figure)** is very strongly associated with HLA-B*1502 in Han Chinese.(14) The marker in Europeans is different viz HLA-A*31:01. (15) These HLA markers can be easily tested for and are now being incorporated into electronic medical records for 'decision support' for prescribers in major Academic Health Centres in the US.



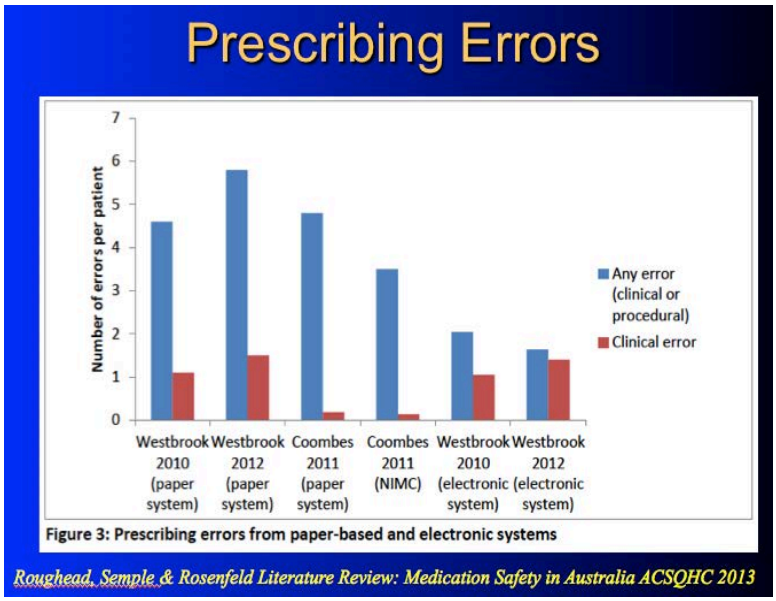
Fein, J. D. et al. N Engl J Med 2005;352:1696

What needs attention?

1. ***Therapeutics education deficiencies***
    a. ***Appreciation of the additional challenges facing people with mental illness***
        i. ***Respect for lived experiences with medication***
    b. ***Gaps revealed in applying the 3 step 'QUM filter'***
    c. ***Seeking and finding help when there is uncertainty in responses to medications***
2. ***Access to quality information regarding medicines for patients with mental illness(16)***
    a. ***Pharmacists***
    b. ***Prescribers***
3. ***Higher level consultative service for patients, GPs and psychiatrists regarding challenging and unusual, cases***
    a. ***Clinical Pharmacology and Therapeutic Drug Monitoring services***
    b. ***Pharmacogenetic expertise and capability***
4. ***eHealth systems that work, connect with each other and are used***

a. ***Effect of eMedication management systems***

b.



References

1. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. N Engl J Med. 2010;363(22):2124-34.
2. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny MP, Sheikh A. Medication Without Harm: WHO's Third Global Patient Safety Challenge. Lancet. 2017;389(10080):1680-1.
3. Roughead EE, Semple SJ, Rosenfeld E. The extent of medication errors and adverse drug reactions throughout the patient journey in acute care in Australia. Int J Evid Based Healthc. 2016;14(3):113-22.
4. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj. 2004;329(7456):15-9.
5. Rose AJ, Fischer SH, Paasche-Orlow MK. Beyond medication reconciliation: The correct medication list. JAMA. 2017;317(20):2057-8.
6. Pevnick JM, Shane R, Schnipper JL. The problem with medication reconciliation. BMJ Quality & Safety. 2016;25(9):726-30.

7. Gur S, Weizman S, Stubbs B, Matalon A, Meyerovitch J, Hermesh H, et al. Mortality, morbidity and medical resources utilization of patients with schizophrenia: A case-control community-based study. Psychiatry Res.260:177-81.
8. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nature Reviews Endocrinology. 2011;8:114.
9. Brett J, Daniels B, Karanges EA, Buckley NA, Schneider C, Nassir A, et al. Psychotropic polypharmacy in Australia, 2006 to 2015: a descriptive cohort study. Br J Clin Pharmacol. 2017;83(11):2581-8.
10. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet. 2017;389(10081):1778-80.
11. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. Bmj. 2014;348.
12. Day RO, Snowden L, McLachlan AJ. Life-threatening drug interactions: what the physician needs to know. Intern Med J. 2017;47(5):501-12.
13. Somogyi AA, Phillips E. Genomic testing as a tool to optimise drug therapy. Australian Prescriber. 2017;40(3):101-4.
14. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011;364(12):1126-33.
15. Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clinical Pharmacology & Therapeutics. 2018:n/a-n/a.
16. Day RO, Snowden L. Where to find information about drugs. Australian Prescriber. 2016;39(3):88-95.