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Short communication

Prevalence and recognition of highly significant medication-smoking cessation interactions in a smoke-free hospital

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ABSTRACT

Background: Some medications are more rapidly metabolized by smokers; upon smoking cessation, medication metabolism may be significantly reduced, resulting in medication-related adverse events. Clozapine, olanzapine and theophylline have been deemed to have potentially highly significant interactions with smoking cessation, which could lead to seizures, extrapyramidal effects and tachycardia, respectively. This study examined the period prevalence and characteristics of patients at risk of highly significant medication-smoking cessation interactions when admitted to a smoke-free hospital.

Methods: A retrospective cross-sectional study was undertaken in an Australian tertiary-referral hospital with a well-established electronic prescribing system. Smokers prescribed clozapine, olanzapine or theophylline prior to and during a hospital admission in 2015 were included. Length of hospital stay, daily doses, and recognition of the potential interaction by treating clinicians were determined from medical records.

Results: The period prevalence of patients at risk of a potentially highly significant medication-smoking cessation interaction was 23/48 (48%), 66/256 (26%) and 1/16 (6%) amongst smokers prescribed clozapine, olanzapine or theophylline, respectively. These interactions were poorly recognized by healthcare professionals during the admission.

Conclusions: Up to one in two patients receiving medications that have potentially highly significant interactions with smoking cessation may be experiencing clinically significant potential interactions. Such interactions, however, were commonly overlooked by hospital staff. Interventions to improve awareness of this issue are warranted.

1. Introduction

One in six people admitted to hospitals are smokers (Szatkowski et al., 2015). Increasingly, hospitals are becoming smoke-free environments. Tobacco smoke interacts with medications via several mechanisms, including induction of cytochrome-P450 enzymes, particularly CYP1A2, activation of the sympathetic nervous system, reduction in blood flow to the skin, and up-regulation of alpha-1-acid glycoprotein production (Zevin and Benowitz, 1999). Whilst many potential interactions are of minimal clinical significance, medications recognized to have most clinically relevant interactions with tobacco smoke are clozapine, olanzapine and theophylline (UK Medicines Information, 2012). As patients stabilized on these specific medications move into a smoke-free environment, health professionals need to consider the impact of changes in smoking habits on therapy and potential adverse events.

Tobacco smoke induction of CYP1A2 increases metabolism of clozapine, olanzapine and theophylline; several case studies have reported increased plasma concentrations due to smoking cessation resulting in seizures, extrapyramidal effects and tachycardia, respectively (Lowe and Ackman, 2010; Rao, 1996). Providing nicotine replacement therapy does not affect nor prevent these interactions, as this therapy does not impact CYP1A2 enzyme activity.

Smoking cessation can produce a reduction in CYP1A2 activity of 20% by day two and 36% by day seven (Faber and Fuhr, 2004). Therefore, patients admitted for a short stay who alter their smoking habits briefly may have reduced potential for clinically significant interactions. On the other hand, if the patient stay exceeds one to two

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days, there is the risk that it may lead to serious adverse events if the interaction is not identified and addressed at the time of admission. Medication-smoking cessation interactions may be less important when these medications are initiated on hospital admission, as clinicians titrate doses to clinical effect. If patients resume smoking after leaving hospital, clinicians need to consider follow-up monitoring and titration of these medications.

Potential interactions may go unrecognized for several reasons. Documentation of smoking status in medical records remains suboptimal in many hospitals (Schofield and Hill, 1999; Smith et al., 2013). Anecdotally, there is limited awareness of the impact of smoking cessation on medications. In hospitals with electronic prescribing, documentation of smoking status and prescribing may not be linked.

Despite the clinical relevance of some medication-smoking cessation interactions, the prevalence of patients at risk for such interactions in smoke-free hospitals has not been documented. The objectives of this study were to determine the period prevalence of patients at risk of potentially highly significant medication-smoking cessation interactions in a smoke-free hospital, characterize those patients, and evaluate health professionals' recognition of such interactions.

2. Methods

A retrospective cross-sectional study was conducted at Austin Hospital, Melbourne, Australia, a 400-bed tertiary-referral public hospital with approximately 33,000 non-same-day admissions and 82,000 emergency department visits in 2015. Austin Health implemented a smoke-free policy in 2009 and has undertaken broad implementation of an electronic medicines management system, Cerner Millennium (Cerner Corporation, Kansas City, MO).

Adult patients were included if they were prescribed clozapine, olanzapine or theophylline prior to and during a hospital admission in 2015 and had a documented history of smoking prior to admission. Patients admitted to the long-term secure extended care mental health ward or the subacute and rehabilitation campuses were excluded. Inpatient prescription of clozapine, olanzapine or theophylline was determined by extracting prescribing data from Cerner Millennium. Medications taken prior to admission were determined by reviewing medical and pharmacist admission notes. For patients prescribed a medication of interest prior to and during the admission, smoking status and demographic parameters were determined by reviewing medical, nursing and pharmacy documentation in the medical records. Whether the interaction was recognized was determined by reviewing pharmacist, medical and nursing notes on admission, mental health unit consultation notes, and discharge summaries.

Period prevalence and characteristics of patients at risk were reported using descriptive statistics. Period prevalence was defined as the proportion of patients who were prescribed clozapine, olanzapine or theophylline prior to and during their hospital admission. These patients were smokers prior to hospitalization and therefore at risk of a medication-smoking cessation interaction upon admission to a smoke-free hospital. Statistical Package for Social Sciences (SPSS) (v.20.0; IBM, Armonk, New York, USA) was used for all analyses. This study was approved by the Austin Health Human Research Ethics Committee (Reference: LNR/16/Austin/119).

3. Results

Olanzapine, clozapine or theophylline were prescribed during 1341 adult admissions in 2015, as detailed in Fig. 1. The period prevalence of patients at risk of a highly significant medication-smoking cessation interaction when prescribed clozapine, olanzapine or theophylline was 23/48 (48%), 66/256 (26%) and 1/16 (6%), respectively. As outlined in Table 1, one-third of admissions of smokers prescribed clozapine were for one or two days, but another one-third were for eight or more days. Over half of the smokers prescribed olanzapine had a length of hospital stay of eight or more days. The one patient with a potential smoking-theophylline interaction was admitted for in excess of eight days. Six patients (26%) at risk of a potential smoking-clozapine interaction and ten patients (15%) at risk of a potential smoking-olanzapine interaction were on relatively high doses at the time of admission to hospital.

Overall, the 90 patients at risk of a medication-smoking cessation interaction had 98 admissions. Twenty-six (27%) admissions were to the mental health unit. Recognition of potential medication-smoking cessation interactions at the time of or during admission by health professionals was poor irrespective of the mental health unit's involvement in the patients' care. Based on documentation in medical records, health professionals recognized potential interactions between tobacco smoke and clozapine in only six cases (25%) and never with olanzapine or theophylline.

4. Discussion

To our knowledge, this is the first study to investigate the period prevalence of patients at risk of potentially highly significant smoking-medication interactions in a smoke-free hospital setting. The clozapine and olanzapine groups had the greatest prevalence of risk of potential interactions. Given the high prevalence of smoking in patients with schizophrenia and that clozapine is prescribed for patients resistant to or unable to tolerate other medications, the high prevalence of clozapine-smoking interaction in this group is not unexpected (de Leon and Diaz, 2005). As theophylline is not first line treatment for chronic obstructive pulmonary disease and asthma, it was to be expected that the prevalence of theophylline-smoking interactions would be low in this group.

The majority of admissions with a potential medication-smoking cessation interaction were for longer than two days, sufficient to establish elevated serum concentrations due to alterations in CYP1A2 activity. Furthermore, many patients were using relatively high daily doses of these medications prior to admission and therefore were at increased risk of developing adverse effects due to smoking cessation.

The incidence of adverse effects due to the medication-smoking cessation interaction could not be determined retrospectively due to the non-specific nature of many adverse effects. These include constipation with clozapine, extra-pyramidal effects with olanzapine and nausea, vomiting and tachycardia with theophylline. Two patients prescribed clozapine prior to and during admission, with no prior history of epilepsy, presented to hospital with infections that may have reduced their smoking over the preceding days. Their emergency department presentations were precipitated by seizures. Two further patients using clozapine also presented with seizures but had a prior history of epilepsy. These seizures were potentially related to alterations in smoking habits in patients on clozapine, but it is not possible to establish a temporal relationship.

Despite good documentation of patients' smoking status, health professionals rarely documented medication-smoking cessation interactions. Even when patients were admitted for several days, the interaction was generally not acknowledged. In addition, when specialist mental health prescribers were involved in patient care, olanzapine and clozapine interactions were still overlooked. For the small number of patients where the clozapine-smoking cessation interaction was recognized, it was usually ward pharmacists or the mental health consultation service who highlighted the issue in the patient notes. Prescriber awareness of theophylline-smoking interaction seems to have waned now that theophylline is rarely prescribed.

Initiatives such as electronic alerts to prescribers, ideally with data linkage of both medications prescribed and smoking status, may help reduce the incidence of smoking-medication interactions and subsequent adverse effects. In settings without electronic prescribing, alerts on dispensing labels or on ward and on dispensary medication shelves may be beneficial.

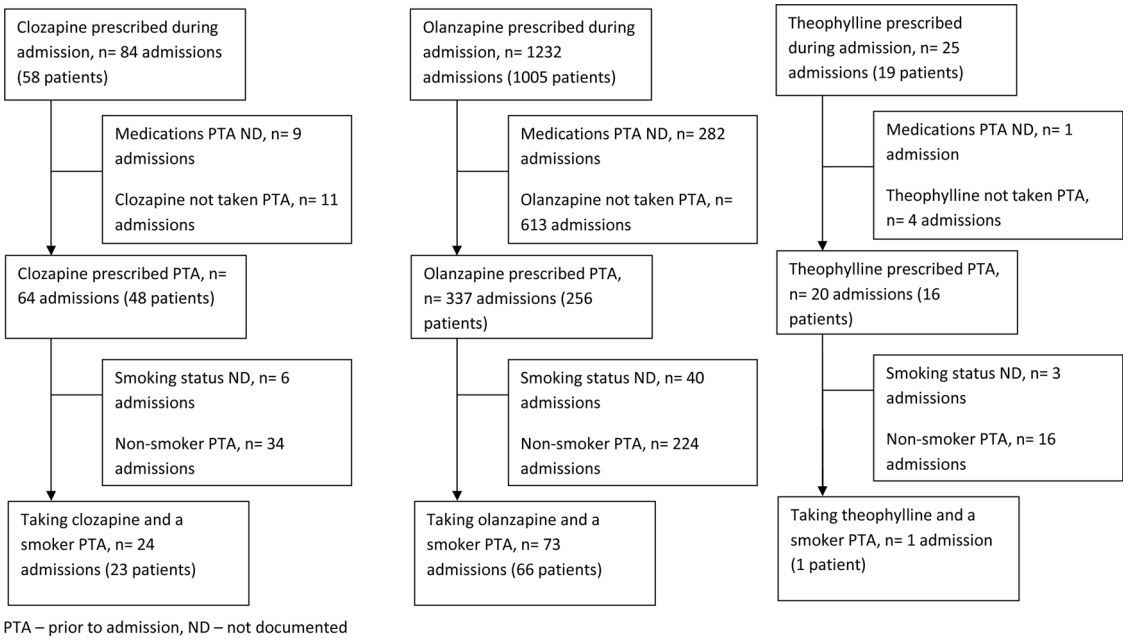

Fig. 1. Flow chart identifying patients at risk for highly significant medication-smoking cessation interactions.
PTA – prior to admission, ND – not documented.

A strength of this study was that all doses of clozapine, olanzapine and theophylline prescribed to all inpatients throughout 2015 were identified, thus providing comprehensive prevalence data. However, this study had several limitations. Patients' smoking statuses on admission and during the hospital stay were not objectively verified due to the retrospective nature of the study. It would be anticipated, however, that the number of cigarettes smoked during hospitalization would be less than prior to admission. Some patients did not have their smoking status documented, and in some cases, there may be inaccuracies in the status documented. We identified potential medication-smoking cessation interactions but did not determine the prevalence of adverse events from these interactions due to the retrospective study design and reliance on medical notes for data capture; this aspect should be investigated prospectively in future studies through patient interviews and observation. The effectiveness of interventions to improve identification and management of these interactions should also be evaluated.

5. Conclusions

In conclusion, this study found that clinically important potential medication-smoking cessation interactions are prevalent in a smoke-free hospital but are frequently overlooked by health professionals. Awareness of clinically important medication-smoking cessation interactions among clinicians and alerts regarding potential interactions may prevent adverse effects.

Table 1
Characteristics of smokers prescribed clozapine, olanzapine or theophylline prior to and during admission.

	Medication of interest prescribed prior to and during hospital admission, n (%)					
	Clozapine (n = 24 admissions)		Olanzapine (n = 73 admissions)		Theophylline (n = 1 admission)	
Age, mean ± s.d.	43 ± 15		48 ± 17		71	
Gender, male	15 (62.5)		48 (65.8)		1 (100)	
Number of regular medicines taken prior to admission, median, [IQR]	7 [4–12]		6 [4–8]		11	
Smoking-related comorbidity						
Cardiovascular	6 (25.0)		17 (23.3)		0 (0)	
Respiratory	6 (25.0)		24 (32.9)		1 (100)	
Cancer	1 (4.2)		6 (8.2)		0 (0)	
Length of hospital stay, days						
≤ 2 days	8 (33.3)		10 (13.7)		0 (0)	
3–7 days	8 (33.3)		26 (35.6)		0 (0)	
≥ 8 days	8 (33.3)		37 (50.7)		1 (100.0)	
Indication for interacting medicine	Schizophrenia	17 (70.8)	Schizophrenia	17 (23.3)	Chronic Obstructive Pulmonary Disease	1 (100.0)
	Schizoaffective disorder	7 (29.2)	Schizoaffective disorder	10 (13.7)		
	Bipolar disorder	0 (0.0)	Bipolar disorder	16 (21.9)		
			Other	30 (41.1)		
Daily dose of interacting medicine prior to admission	< 200 mg	1 (4.2)	< 10 mg	14 (19.2)	240 mg	1 (100.0)
	200–600 mg	17 (70.8)	10–20 mg	44 (60.3)		
	> 600 mg	6 (25.0)	> 20 mg	10 (13.7)		
			Pro re nata (PRN)	4 (5.5)		
			Not documented	1 (1.4)		

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Contributors

ST and JG designed the study. CC collected data. Analyses were performed by ST and CC. ST and CC led the drafting of the manuscript. JG and DT revised the manuscript. All authors have contributed to and have approved the final manuscript.

Conflict of interest

ST and JG have held an investigator-initiated research (IIR) grant from Pfizer focusing on hospital pharmacist-initiated smoking cessation interventions for hospitalized smokers. JG holds an IIR grant from Boehringer-Ingelheim. No other disclosures are reported.

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