

# Potential drug-drug interactions with phentermine among long-term phentermine consumers: A retrospective analysis

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**Background.** Phentermine is an internationally recognised amphetamine derivative with significant appetite-suppressing properties. The drug is indicated for the short-term management of obesity, as the long-term (LT) use of phentermine may potentially be associated with severe cardiovascular side-effects, abuse and dependence. The LT use hereinafter describes periods exceeding 12 consecutive weeks. This use may also be associated with potential drug-drug interactions (PDDIs), which may result in adverse drug reactions (ADRs). The literature reports that phentermine is often prescribed LT and for several other off-label indications, increasing the risk for individuals to experience adverse drug events (ADEs) and drug-drug interactions (DDIs). There are, to our knowledge, no South African (SA) studies investigating the prevalence of co-prescribing LT phentermine with drugs that may potentially cause DDIs.

**Objective.** To determine the prevalence of mild, moderate and severe DDIs with phentermine use when the duration of therapy in private healthcare exceeded 12 consecutive weeks.

**Methods.** A cross-sectional drug utilisation review (DUR) was done by using data obtained from a SA pharmacy benefit management (PBM) company's database. Retrospective data of medicine claims for phentermine, from 1 January 2015 to 31 December 2019, were extracted for analysis. The number of days phentermine was supplied was used to identify the study population, in other words, those patients who received the drug LT. A drug interaction checker (Drugs.com) was used to identify potential mild, moderate and severe DDIs when using phentermine and co-prescribed drugs concurrently.

**Results.** A total of 889 patients received phentermine LT. The top 20 drugs identified as being frequently co-prescribed in this study population demonstrated no mild PDDI, 15 (75%) moderate PDDIs and 5 (25%) severe PDDIs. The most common co-prescribed drug in the moderate group was dextromethorphan ( $n=282$ , 31.72%) and the least co-prescribed was formoterol ( $n=52$ , 5.85%). Among the drug group 'severe PDDIs', tramadol ( $n=416$ , 46.79%) was most frequently prescribed, whereas phenylpropanolamine ( $n=69$ , 7.76%) was the least prescribed to patients in this group.

**Conclusion.** There are patients who receive LT phentermine therapy despite the potential severe consequences that may result. These patients may receive concomitant therapy with phentermine and other pharmaceutical constituents, which may potentially cause DDIs, more specifically, moderate and severe DDIs. As such, these patients are not only confronted with the consequences of DDIs but are also at risk to experience ADRs as the residual effect of PDDIs.

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Phentermine, an extraordinary amphetamine derivate, is South Africa (SA)'s most popular prescription-only anti-obesity medication used for its appetite-suppressing properties.<sup>[1-3]</sup> The drug stimulates the central nervous system (CNS), inhibiting the reuptake and stimulating the release of endogenous neurotransmitters, including dopamine (DA), serotonin (5-HT) and norepinephrine (NE).<sup>[4-6]</sup> Consequently, there is an increase in the concentration of these neurotransmitters in the CNS and stimulatory effects.<sup>[4,5]</sup> In the brain, the increased DA concentration will provide a constant DA-induced feeling/sensation of reward (associated with eating), which will result in appetite suppression.<sup>[5,7]</sup> Persistent 5-HT neurotransmission in the brain may also result in appetite suppression; however, these effects are only achieved at doses higher than the recommended maximum daily dosage, that is >30 mg phentermine.<sup>[8,9]</sup> Once NE is released, the hormone cascade of the hypothalamus-pituitary axis (HPA) is activated via the amygdala of the brain.<sup>[10-12]</sup> Signals are transmitted from the amygdala to the hypothalamus, then to the pituitary gland, and finally to the adrenal cortex, positioned on top of the kidneys.<sup>[12,13]</sup> As a result, DA, NE and epinephrine are released into the bloodstream, where they will bind to adrenergic receptors ( $\alpha$  and  $\beta$  receptors) of fat tissue and smooth muscles.<sup>[13,14]</sup>

The stimulatory effects of DA and NE will enhance the breakdown of fat tissue, consequently resulting in weight loss.<sup>[14-16]</sup> Epinephrine will result in increased blood glucose concentrations: the individual will feel satiated, and the appetite is suppressed.<sup>[10,15,16]</sup> Unfortunately, the effects of these catecholamines are not limited to the abovementioned desired effects, as these hormones bind to multiple adrenergic receptors located throughout the body.<sup>[17]</sup> As such, an individual may experience some undesired effects, also known as side-effects.<sup>[17,18]</sup> The most common side-effects of phentermine are dry mouth and insomnia,<sup>[19,20]</sup> as phentermine is generally used short-term (ST),<sup>[2,21]</sup> in other words not longer than 12 consecutive weeks.<sup>[22]</sup> It is recommended that phentermine not be used for longer than 12 consecutive weeks (hereinafter referred to as long-term (LT)), as LT use (off-label indication for the drug) may be associated with severe cardiovascular side-effects, abuse and dependence.<sup>[23,24]</sup> The increase in the blood concentration of DA and NE will also increase the stimulatory effects of the heart,<sup>[15,16,25,26]</sup> kidneys<sup>[15,16]</sup> and blood vessels,<sup>[25,26]</sup> which may result in heart rate irregularities (tachycardia, arrhythmias and palpitations) and hypertension.<sup>[23,27-31]</sup> The increase in the stimulatory effects of the CNS may also result in drug abuse, dependence<sup>[23,28]</sup> and seizures,<sup>[23]</sup> or trigger DA-induced hallucinations or episodes of psychosis.<sup>[16-23]</sup> The LT use of phentermine may, theoretically, cause

significant harm to patients; the US Food and Drug Administration (FDA) therefore restricted the duration of this medicine's use to ST use.<sup>[3,23]</sup>

The LT use of phentermine is permitted, provided the drug is administered as the FDA-approved, fixed-dose combination phentermine/topiramate.<sup>[32]</sup> This is also the only instance in which phentermine may be combined with other pharmaceutical preparations for the treatment of obesity.<sup>[32,33]</sup> The success of this drug combination can be attributed to a moderate drug-drug interaction (DDI) between phentermine and topiramate.<sup>[28]</sup> Moderate DDIs are classified as such, since they may cause distinctively stressful or intolerable adverse drug reactions (ADRs) in individuals.<sup>[34]</sup> Topiramate is an anti-epileptic that can, in its own capacity, induce weight loss, and if administered together with phentermine, increase the plasma concentration thereof and thus also the efficacy.<sup>[28,33,35]</sup> However, as it increases the plasma concentration of phentermine, it may also increase the adverse effects thereof, such as tachycardia, increased blood pressure levels and palpitations.<sup>[35]</sup> Evidently, no matter how successful this combination may be, there are risks associated with it that may potentially be harmful to individuals. This drug combination is not available in SA.

Not all DDIs are as beneficial as the use of phentermine/topiramate, and some may, depending on the severity, cause significant harm to individuals.<sup>[36]</sup> Consequently, not only is the LT use of phentermine not recommended, but also the simultaneous use of phentermine with drugs that may potentially cause mild, moderate or severe DDIs.<sup>[23,35]</sup> The patient information leaflet (PIL) of the drug warns against the simultaneous use of phentermine with other pharmaceutical preparations, including sympathomimetics, selective serotonin reuptake inhibitors (SSRIs), oral hypoglycaemic preparations and antihypertensive and epileptogenic agents, as the simultaneous use thereof may result in DDIs and thus ADRs.<sup>[23,35]</sup> Unfortunately, it is not uncommon for phentermine to be administered concurrently with preparations intended to lower blood glucose and blood pressure levels, as the drug is indicated for the treatment of obesity, which is commonly associated with diabetes and/or cardiovascular diseases such as hypertension.<sup>[23,37]</sup> Additionally, it is likely for phentermine to be used LT and in combination with pharmaceutical preparations that may cause DDIs.<sup>[24]</sup> There is, to our knowledge, no SA study investigating the prevalence of potential drug-drug interactions (PDDIs) among patients receiving LT therapy with phentermine. The objective of this study was therefore to determine the prevalence of potentially mild, moderate and severe DDIs with phentermine when the duration of therapy (DOT) in the private healthcare sector of SA exceeded 12 consecutive weeks.

## Methods

### Study design

A descriptive, retrospective, quantitative drug utilisation review (DUR) study design was used, making use of longitudinal patient medicine claims data from a SA pharmacy benefit management (PBM) company's database.

### Study setting and data source

The study was conducted in the private healthcare sector of SA, using approved and paid medicine claims data for phentermine from 1 January 2015 to 31 December 2019. The data comprised dispensing information from all SA pharmacies across all provinces in SA, as the PBM is linked to all pharmacies in SA and 98% of dispensing practitioners. The data fields from all patient records used included the date the prescription was issued, the number of days the drug was provided for, the information on the dispensed product (including

the active ingredient), the National Pharmaceutical Product Index (NAPPI) code, and the gender and age of the patient. Each patient medication record was assigned a random number to mask the identity of the patient.

### Study population

The study population comprised all patients on the PBM company's database who received phentermine LT from 1 January 2015 to 31 December 2019. A grace period of 5 days was given for early/late collection of prescriptions. Data comprising the NAPPI codes 721786-006 (15 mg phentermine) and 721794-009 (30 mg phentermine) were analysed. Information on gender and age was used to interpret the demographic results of patients receiving LT therapy with phentermine. Based on their gender, patients were considered either female or male.

### Data analysis

The data were analysed by the director of Medicine Usage in South Africa (MUSA), Faculty of Health Sciences at the North-West University (NWU), Potchefstroom, SA. Descriptive statistics were used to explain and interpret the data spread, and included frequencies and percentages. The frequency and percentage were used to numerise the demographic information of those patients receiving phentermine LT. A list of drugs co-prescribed to patients receiving phentermine LT was also extracted for analysis. A drug interaction checker from Drugs.com was used to identify the drugs that may potentially cause a mild, moderate or severe DDI when co-prescribed with phentermine.<sup>[36]</sup> Mild DDIs are those interactions that may cause some discomfort in individuals, but do not require change in therapy and are of little clinical significance.<sup>[34,38]</sup> Moderate DDIs, however, may cause distress, are of moderate clinical significance and usually require change in therapy.<sup>[34,38]</sup> Severe DDIs may have life-threatening repercussions and are therefore of major clinical significance and require change in therapy.<sup>[34,38]</sup> The top 20 drugs that may cause PDDIs and are most frequently prescribed to patients receiving phentermine LT were listed accordingly. The potential ADRs that may occur between such DDIs were also listed.

### Ethics

Through a contractual agreement, the PBM company's board of directors has consented to the research entity MUSA accessing and using their database if the data are intended for research purposes. As such, the researchers were permitted, through the PBM company's consent, to use the company's data for this study. A confidentiality agreement was signed by the researchers involved and the director of MUSA prior to gaining access to the database. The PBM company's name was therefore not disclosed throughout the study in order to ensure that confidentiality and anonymity are maintained. All patient records were de-identified, that is, any personal information of the patients, medical schemes or prescribers was depersonalised prior to the researchers accessing the database. Each patient record was therefore assigned a random 'dummy' member number; this ensured that confidentiality and anonymity were maintained throughout the study. The Health Research Ethics Committee of the Faculty of Health Sciences of the NWU, Potchefstroom campus, granted ethical approval to conduct the study (ref. no. NWU-00179-14-A1-11).

### Results

The study population consisted of 889 patients on the medicine claims database who received LT therapy with phentermine during the study period. Of these patients, most were female (775, 87.18%) and aged 35 - 59 years ( $n=602$ , 67.72%). The top 20 drugs that

were most commonly co-prescribed with phentermine, which may potentially have caused a DDI among these LT phentermine consumers, are summarised in Table 1. The drugs are listed in descending order according to the number of people who received the respective co-prescribed drugs. The table also gives the ADRs that may have resulted from a PDDI between phentermine and the relevant co-prescribed drugs.

As seen from the results in Table 1, there were 15 (75%) drugs that may potentially have caused a moderate DDI with phentermine. The remainder of the drugs ( $n=5$ , 25%) may potentially have caused a severe DDI.

### Prevalence of potential DDIs with phentermine among patients receiving the drug LT

The data were analysed to determine the prevalence of co-prescribing of phentermine with drugs that may potentially cause mild, moderate and severe DDIs among patients receiving phentermine LT.

### Prevalence of potentially mild DDI

According to the data, there were no PDDIs that were mild to severe among the patients receiving phentermine LT.

### Prevalence of potentially moderate DDIs

Results indicated that dextromethorphan ( $n=282$ , 31.72%) was the drug most frequently prescribed to patients receiving phentermine LT that may potentially have caused moderate DDIs. Thereafter, ephedrine ( $n=232$ , 26.10%) was most frequently prescribed, followed by salbutamol ( $n=196$ , 22.05%) and metformin ( $n=185$ , 20.81%). The drug that was least prescribed to patients in this group was formoterol ( $n=52$ , 5.85%). Other drugs co-prescribed with phentermine that may potentially have caused moderate DDIs are given in Table 1.

### Prevalence of potentially severe DDIs

The most common drug prescribed together with phentermine was tramadol, which means that 46.79% ( $n=416$ ) of patients receiving phentermine LT potentially experienced severe DDIs with tramadol. The second drug was escitalopram ( $n=99$ , 11.14%), followed by fluoxetine ( $n=81$ , 9.11%) and sertraline ( $n=75$ , 8.44%). Phenylpropanolamine was the drug least prescribed to patients ( $n=69$ , 7.76%) in this category.

### Discussion

This is the first SA study to investigate the prevalence of PDDIs with phentermine when the recommended DOT exceeded 12 consecutive weeks. The study revealed that a total of 889 patients from the private healthcare sector in SA received phentermine LT. In other words, from 1 January 2015 to 31 December 2019, there were 889 patients on the database who received phentermine LT despite this use not being recommended.<sup>[23]</sup> The LT use of phentermine is not advised, since there are no data supporting its use and it may potentially be associated with severe cardiovascular side-effects (including tachycardia and hypertension), abuse and dependence.<sup>[19-24]</sup> DDIs may also occur among patients who receive the drug LT, thereby increasing the risk for ADRs to occur.<sup>[24]</sup>

Analysis of the top 20 drugs that were co-prescribed with phentermine and may potentially have caused a DDI indicates that these drugs may potentially have caused moderate and severe DDIs. There were no drugs co-prescribed with phentermine that may potentially have caused mild DDIs (e.g. evening primrose oil). It may therefore be deduced that patients receiving LT therapy with phentermine may potentially have experienced moderate and severe DDIs.

The drugs co-prescribed with phentermine that may possibly have caused moderate DDIs are listed in Table 1. There were 282 (31.72%) patients who received phentermine together with the opium

**Table 1. Frequency of potential drug-drug interactions between phentermine and co-prescribed drugs**

Active ingredient	Frequency, <i>n</i> (%)	Severity of drug-drug interaction	Adverse drug reaction
Tramadol	416 (46.79)	Severe	Seizures
Dextromethorphan	282 (31.72)	Moderate	Serotonin syndrome
Ephedrine	232 (26.10)	Moderate	Hypertension, tachycardia
Salbutamol	196 (22.05)	Moderate	Hypertension, heart rate irregularities
Metformin	185 (20.81)	Moderate	Hypoglycaemia
Amitriptyline	177 (19.91)	Moderate	Hypertension, arrhythmias, tachycardia
Phenylephrine	152 (17.10)	Moderate	Hypertension, tachycardia
Levothyroxine	132 (14.85)	Moderate	Cardiac insufficiency (tachycardia, arrhythmias, palpitations)
Pseudoephedrine	126 (14.17)	Moderate	Hypertension, tachycardia
Thyroxine	118 (13.27)	Moderate	Cardiac insufficiency (tachycardia, arrhythmias, palpitations)
Escitalopram	99 (11.14)	Severe	Serotonin syndrome
Promethazine	94 (10.57)	Moderate	Psychosis, arrhythmias
Preparations containing alcohol	94 (10.57)	Moderate	Cardiovascular side-effects, including tachycardia
Fluoxetine	81 (9.11)	Severe	Serotonin syndrome
Salmeterol	77 (8.66)	Moderate	Hypertension, heart rate irregularities
Sertraline	75 (8.44)	Severe	Serotonin syndrome
Prochlorperazine	71 (7.99)	Moderate	Psychosis, arrhythmias
Phenylpropanolamine	69 (7.76)	Severe	Life-threatening cardiac complications (pulmonary hypertension)
Topiramate	65 (7.31)	Moderate	Hypertension, tachycardia, palpitations
Formoterol	52 (5.85)	Moderate	Hypertension, heart rate irregularities

alkaloid<sup>[3]</sup> dextromethorphan, which is used as a cough suppressant and is a weak 5-HT reuptake inhibitor.<sup>[3,35]</sup> As previously discussed, phentermine may also increase 5-HT concentration in the CNS.<sup>[8,9]</sup> Therefore, if administered together, phentermine may potentiate the effects of dextromethorphan, thereby potentially causing a moderate DDI.<sup>[35]</sup> Consequently, excessive nerve cell activity and life-threatening symptoms (e.g. high blood pressure and temperature) may surface, a condition also known as serotonin syndrome (5-HT syndrome).<sup>[6,8,19,39,40]</sup> As such, patients receiving LT therapy with phentermine may potentially have experienced 5-HT syndrome as the residual effect of a moderate DDI between phentermine and dextromethorphan.

Phentermine may potentially cause a moderate DDI with ephedrine, pseudoephedrine and phenylephrine as well. Pseudoephedrine and phenylephrine are used as systemic decongestants, whereas ephedrine is used as a pressor agent for low blood pressure (hypotension).<sup>[3]</sup> These agents, as with phentermine, stimulate adrenergic receptors in the body and, if administered together, phentermine can potentiate the adrenergic response to these agents.<sup>[3,35]</sup> As such, these drugs will add to the stimulatory effects of the heart, kidneys and blood vessels, which will further increase the blood pressure levels and heart rate.<sup>[35]</sup> Patients may therefore experience hypertension and tachycardia (increased heart rate) as the result of PDDIs between phentermine and these agents.<sup>[35]</sup> Phentermine may also potentiate the adrenergic response to salbutamol, salmeterol and formoterol. These agents also stimulate adrenergic receptors, and are indicated for the treatment of asthma and chronic obstructive pulmonary disease.<sup>[3]</sup> Therefore, patients who received phentermine together with salbutamol ( $n=196$ , 22.05%), salmeterol ( $n=77$ , 8.66%), or formoterol ( $n=52$ , 5.85%) may potentially have experienced hypertension and/or heart rate irregularities.<sup>[15]</sup>

Approximately 21% of patients who received phentermine LT also received metformin, a biguanide designed to lower the blood glucose levels.<sup>[3]</sup> Metformin is indicated for the treatment of obesity among diabetic individuals, as it provokes mild anorexia and therefore assists in controlling weight gain.<sup>[3]</sup> As previously discussed, phentermine increases the concentration of NE in the bloodstream and consequently also the blood glucose levels.<sup>[14,26]</sup> As such, these constituents oppose each other's mechanism of action, thereby potentially causing a moderate DDI. However, this is not the mechanism through which the ADR hypoglycaemia occurs.<sup>[35]</sup> Phentermine initially causes an increase in blood glucose levels, resulting in appetite suppression and consequently also weight loss.<sup>[14,15,26]</sup> Weight loss may have an impact on glycaemic control, as it lowers blood glucose levels.<sup>[35]</sup> Therefore, since metformin and phentermine lower the blood glucose levels and the last-mentioned medicine causes weight loss, administering these drugs together may have additive effects that may potentially result in hypoglycaemia.<sup>[14]</sup> In this instance, hypoglycaemia may commonly present with adrenergic neurogenic signs and symptoms such as anxiety, tremors and palpitations.<sup>[41]</sup>

Moreover, the use of phentermine together with amitriptyline, a tricyclic antidepressant, may cause moderate DDIs that may potentially result in hypertension, arrhythmias and/or tachycardia.<sup>[3,35]</sup> Amitriptyline is indicated for the management of depressive disorders and the drug acts by inhibiting the reuptake of NE.<sup>[3,35]</sup> Consequently, administering phentermine together with this pharmaceutical constituent may further increase the concentration and stimulatory effects of NE, because phentermine (as previously discussed) also increases NE concentration.<sup>[9,35,42]</sup> Therefore, patients who received these two agents simultaneously ( $n=177$ , 19.91%) may potentially have experienced the abovementioned ADRs as the residual effect of potentially moderate DDIs.

The thyroid hormones, levothyroxine and thyroxine, are indicated for hypothyroidism, a medical disease in which the thyroid hormone produces insufficient amounts of the hormone thyroxine.<sup>[3,43]</sup> The thyroid gland co-operates with the adrenal glands to release NE into the bloodstream in order to ensure that the body's metabolism works sufficiently.<sup>[44,45]</sup> Administration of these thyroid hormones will stimulate the adrenal gland to release NE into the bloodstream, and administering phentermine together with these hormones will have additive effects.<sup>[46]</sup> The net result will be excessive concentrations of NE in the bloodstream, which may potentially result in cardiovascular side-effects such as tachycardia, arrhythmias and palpitations.<sup>[46]</sup> Phentermine may also cause a moderate DDI with preparations containing alcohol, as alcohol potentiates the CNS and cardiovascular effects of phentermine.<sup>[35]</sup>

There were 94 (10.57%) and 71 (7.99%) patients receiving phentermine together with promethazine and prochlorperazine, respectively. These pharmaceutical agents are indicated, among other indications, for the treatment of nausea and vomiting.<sup>[3,35]</sup> Promethazine and prochlorperazine supposedly oppose the dopaminergic activity of phentermine, which may reduce the weight-reducing properties of the drug.<sup>[35]</sup> Phentermine is expected to reduce the neuroleptic efficacy and potentiate the arrhythmogenicity of these agents, which may cause psychosis and arrhythmias, respectively.<sup>[35]</sup> Additionally, phentermine may also exacerbate pre-existing symptoms of psychosis.<sup>[35]</sup> As such, the mechanism of the PDDI is based on the fact that these agents may oppose the pharmacological effects of phentermine, and vice versa.

Lastly, 65 (7.31%) patients received phentermine together with the anti-epileptic topiramate, and may therefore have experienced moderate DDIs. The combination phentermine/topiramate was approved by the FDA in 2012 for the LT management of obesity, as these constituents have proven to cause significantly more weight loss when combined than when each agent is used individually as monotherapy.<sup>[32,47,48]</sup> The precise mechanism of interaction between phentermine and topiramate has not been determined yet; however, it is known that topiramate increases the plasma concentration of phentermine and therefore also its efficacy.<sup>[14]</sup> It is also known that weight loss is a common side-effect of topiramate, thereby adding to phentermine's weight-reducing effects if the two are administered simultaneously.<sup>[32]</sup> Individuals may also experience more intense adverse effects caused by the increased plasma concentration of phentermine, for example tachycardia, increased blood pressure levels and palpitations.<sup>[35]</sup> Nevertheless, the FDA has approved this drug combination as it has been proven to be safe and effective.<sup>[48]</sup> Regrettably, this combination is not available in SA yet.<sup>[33]</sup>

Furthermore, patients receiving LT therapy with phentermine also received drugs that may potentially have caused severe DDIs with phentermine (Table 1). Approximately 50% ( $n=416$ , 46.79%) of patients in the study population potentially experienced severe DDIs with phentermine and tramadol. Tramadol is indicated for the management of moderate and severe pain, and acts by inhibiting the reuptake of 5-HT.<sup>[3]</sup> The use of phentermine and tramadol is not recommended, since phentermine can lower the threshold for convulsions and tramadol may sometimes cause seizures.<sup>[33,35]</sup> The combination of these epileptogenic agents may have additive effects, potentially causing a medical emergency and causing significant harm to an individual.<sup>[28,51]</sup>

The PIL of phentermine warns explicitly against the simultaneous use of the drug with SSRIs, as these drugs inhibit serotonin metabolism and may be associated with cardiac valvular disease.<sup>[23]</sup> The drugs are mainly indicated for depressive disorders,<sup>[3]</sup> and there were 99 (11.14%), 81 (9.11%) and 75 (8.44%) patients receiving



phentermine together with escitalopram, fluoxetine and sertraline, respectively. The combination of phentermine with SSRIs may result in 5-HT syndrome and should be avoided, given its severity.<sup>[35,40]</sup>

As seen from Table 1, the simultaneous use of phentermine with phenylpropanolamine may also result in life-threatening complications.<sup>[28,35]</sup> In a case-control epidemiological study, the use of anorexigenic agents such as phenylpropanolamine and phentermine may be correlated with a greater risk for pulmonary hypertension.<sup>[35]</sup> Therefore, if these agents were to be used simultaneously, their combined effects on the cardiovascular system may cause life-threatening cardiac complications.<sup>[35,52]</sup> Evidently, given the severity of the potential ADRs that may result from these PDDIs, such interactions require instant medical attention and a change in therapeutical regimens.<sup>[38]</sup>

### Study limitations

The present study is not without limitations. Firstly, it only included approved and paid claims for phentermine and excluded cash paid claims; therefore, the actual number of patients in the study population could not be accurate. Secondly, the total number of patients receiving phentermine LT could potentially be miscalculated, since the analysis of the duration of use was limited to the study period and the number of patients in the database. The abovementioned is also applicable to the prevalence of PDDIs with phentermine. Only one drug interaction checker was used to identify drugs that may potentially cause DDIs with phentermine; therefore, other PDDIs could possibly exist. The study investigated the prevalence of PDDIs and it could therefore not be known for sure if the patients actually experienced a DDI. Furthermore, the data reflected the dispensing information of phentermine; the actual consumption patterns of the drug could not be known for sure, as there was no evidence that these patients in fact consumed the phentermine. Lastly, the analyses were done with the understanding that the data obtained from the PBM company's database were precise and reliable.

### Conclusion

Phentermine is the most frequently used anorexigenic appetite suppressant in SA, and the drug's popularity can be owed to its judicious use.<sup>[19,21,22]</sup> The DOT with the drug was restricted in 1977 to ST use only, as there were concerns that the LT use of phentermine may be associated with severe cardiovascular side-effects.<sup>[49,53]</sup> To this day, the DOT with phentermine remains restricted to periods not surpassing 12 consecutive weeks, as no evidence has been provided to support the safety and effectiveness of LT therapy.<sup>[49,53]</sup> Nonetheless, the results from this study indicate that prescribers in the private healthcare sector of SA prescribe phentermine off-label LT despite the potentially severe consequences. The results also indicate that these prescribers combine LT therapy with phentermine with other drugs such as SSRIs, despite the PIL advising against this.<sup>[23]</sup> The PIL of phentermine specifically warns against such a drug combination, as these drugs may have harmful interactions that may cause PDDIs and ADRs.<sup>[23,50]</sup> It is evident from the study results that the patients who received LT therapy with phentermine were also at risk to experience other potentially moderate and severe DDIs, and as one can see from Table 1, the potential ADRs that may have occurred from these PDDIs seem rather severe. This raises the following concern: why would prescribers put their patients at risk of potentially experiencing such ADEs? It also raises the question of whether a proper benefit-to-risk analysis was done prior to initiating pharmacotherapy with phentermine. These aspects deserve further investigation.

To conclude, patients receiving LT therapy with phentermine in the private healthcare sector of SA are at risk of experiencing moderate to severe DDIs. The ADRs that may occur from these PDDIs are rather serious, and may be harmful to the patients involved. Prescribers should be more vigilant in the co-prescribing of phentermine with other drugs that may potentially cause DDIs. These prescribers should also be made aware of the label indications of phentermine, as they are provided to assist in the rational and safe prescribing of the drug so that DDIs and ADRs can be prevented.

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