Title: Dose adjustment guidelines for medications in patients with renal impairment: How consistent are drug information sources?

Short title: Consistency in renal drug dosing guidelines

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Abstract

Background: It is known that patients with renal disease are often administered inappropriate dosages of drugs. A lack of quantitative data in the available drug information sources and inconsistency in dosing information may augment the problem of dosing error.

Aims: To determine the concordance among five drug information sources regarding the dosing recommendations provided for drugs considered problematic in patients with renal impairment and to determine the consistency among the sources regarding the definition of renal impairment and categorisation of chronic kidney disease.

Methods: Five standard drug information sources were reviewed for 61 drugs recommended to be used with caution in renal impairment. Information on recommendations for dosage adjustment in renal impairment was extracted and analysed. Further, the definition and classification of renal impairment were recorded. The recommendation for each drug was coded into six different categories and the inter-source reliability was calculated.

Results: Only slight agreement was observed among the sources (Fleiss Kappa: 0.3). Qualitative data were not well defined and there was a lack of consistency in quantitative values. Some drugs marked as contraindicated in one source were not mentioned as such in others. Also, drugs considered as not requiring dosage adjustment in one source had explicit recommendations in other sources. The definition and classification of renal impairment differed among the five information sources.

Conclusions: There should be an evidence-based approach to drug dosage adjustment in order to bring uniformity to the recommendations. Regular updating of the content of the drug information sources is also important.

Key words: renal impairment, dosage adjustment, drug prescribing, guidelines, kidney disease

Introduction

Chronic kidney disease (CKD) is a long-term health condition where a person has reduced renal function, with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2, lasting for 3 months or more.[1] The prevalence of CKD increases disproportionally in older people due to age-related physiological changes in renal function, alongside the increasing prevalence of other conditions such as diabetes and cardiovascular disease.[2,3]

Impaired renal function can have pronounced effects on the pharmacokinetics of many drugs as a result of alterations in glomerular filtration, tubular secretion, reabsorption or metabolism.[4] Therefore, there is an increased risk of drug-related problems (DRPs) such as the use of contraindicated drugs and inappropriate doses, with potential adverse outcomes.[5,6] It is essential to select the proper drug and individualise the dosage in order to avoid the occurrence of adverse events.[7] Previous studies have reported that 20-67% of prescriptions for patients with impaired renal function contain errors.[8-12] The asymptomatic nature and opportunistic diagnosis of CKD is one of the reasons for the higher prevalence of inappropriate prescribing.[13,14] Other contributing factors reported include prescribers' poor knowledge of medications requiring dosage adjustment, the presence of renal impairment being overlooked by prescribers, underestimation of potential adverse events, and the lack of evidence-based data to guide prescribers on precautions and dosage adjustments.[15-17] Moreover, a lack of quantitative data in the available drug information sources, and

contradiction and inconsistency in dosing information may augment the problem of dosing error.[18]

In Australia, the *Australian Medicines Handbook* (AMH)[19] or the product information provide recommendations for dosage adjustment in renal impairment. Other international resources commonly accessible include the *British National Formulary* (BNF)[20] and the *American Hospital Formulary System* (AHFS).[21] However, despite their availability, significant practice gaps have been reported in prescribing for patients with renal impairment.[22]

The purpose of this study was to systematically compare the recommendations for dosage adjustment in renal impairment among different drug information resources. We consulted the AMH (2012), Monthly Index of Medical Specialties[23] (MIMS; 2012), BNF (2012), AHFS (2012) and a specialised text, *Drug Prescribing in Renal Failure*[24] (DPRF; 2007), for a range of drugs that are known to be problematic when used in patients with renal impairment. The specific objective was to determine the consistency among the sources in dosing recommendations provided for individual drugs and in the definition of renal impairment and categorisation of CKD.

Methods

This systematic comparison included data extracted for 61 drugs recommended as to be used with caution in patients with renal impairment by the Department of Veterans' Affairs (DVA), Australia (Appendix 1).[25] Recommendations for dose modification in renal impairment for each of the 61 drugs were extracted from the five sources. When a drug had more than one brand available in MIMS, only one brand was chosen randomly for analysis. Data extraction also included the definitions and categorisation of renal impairment in each of

the five sources. One researcher (AK) extracted the data, which was reviewed independently by another researcher (RC).

The definitions and categorisation of renal impairment reported in each of the five sources were compared to determine consistency. The recommendations for dose modification extracted from the five sources were allocated into six categories using an adaptation of the categorisation described by Vidal et al, as follows.[18]

1. Contraindicated (CI): This category included drugs that were recommended to be avoided in renal impairment of any severity. For example, the AHFS recommended that "metformin alone or in fixed combination with other drugs is contraindicated in renal impairment."
2. Missing (M): This category included drugs that were not included in the information source. For example, AHFS contained no information on vildagliptin and strontium ranelate.
3. Numerical recommendations (N):
   - Dose modification is recommended based on creatinine clearance (CrCl) calculated by Cockcroft-Gault (CG) formula[26] or eGFR/serum creatinine (SCr) value. For example, AMH recommended a maximum daily dose of 50mg for sitagliptin in patients with CrCl between 30-50mL/min and 25mg for patients with CrCl of less than 30 mL/min.
   - Dose modification based on CrCl/eGFR/SCr is not mentioned but there is a clear recommendation to avoid the drug below a certain range of CrCl/eGFR/SCr value. For example, AMH recommended teriparatide to be avoided in patients having a CrCl below 30 mL/min.
4. Non-Numerical recommendations (NN):

- *Recommendations that were ambiguous.* For example, the recommendation for metoclopramide in the BNF was to avoid or use small doses in severe renal impairment.
- *Did not mention the eGFR/CrCl value/severity of renal impairment for which the drug had to be avoided or reduced*. For example, the recommendation for topiramate in AMH included "reduced maintenance dose and longer interval between dose adjustments may be needed in renal impairment as it takes longer to reach steady state concentrations". Further, phrases like "avoid in severe impairment" in MIMS and AHFS were considered as non-numeric recommendations as these sources did not pre-define "severe renal impairment". However, if these sources mentioned the CrCl/eGFR range next to the severity of renal impairment, then such recommendations were considered to be numeric recommendations.
- *Use with caution.* The drug information sources mentioned one of the following statements but failed to give the specific recommendation for dose adjustment based on the CrCl/eGFR/SCr value: "careful monitoring of dose is required"; "monitor the drug serum concentration"; "monitor for side effects". For example, AHFS recommended that "particular attention to close monitoring of methotrexate is recommended for patients with renal impairment."
- *Did not specify the required dose for the particular stage of renal impairment*. For example, the recommendation for enoxaparin in BNF was "risk of bleeding increased; reduce dose if eGFR less than 30 mL/minute/1.73 m^2 - consult product literature for detail."

5. No advice mentioned (X): The drug monograph was present in the information source but there was no information on its use in patients with renal impairment. For

example, the monograph for vardenafil in AMH contained no information regarding dose adjustment in patients with renal impairment.

6. Dosage adjustment not required (Y): The information source advised to give the normal drug dose in renal impairment. For example, the DPRF recommended that dose adjustment for bupropion is not required.

For the purpose of analysis, the 6 categories of recommendations were coded numerically to assign computable values with CI =1, M=2, N=3, NN=4, X=5 and Y= 6, respectively. The concordance in dosing recommendation for all 61 drugs among the different sources was calculated using Fleiss Kappa (K).[27-29] The concordance was determined in two approaches using REcal, an inter-coder reliability web service.[30] In the first approach, concordance was calculated for the 34 drugs that had information in all five sources, excluding drugs that were missing from one or more sources. In the second analytical approach, the DPRF book was excluded, as it was an older publication, and the concordance was determined for the 54 drugs included in all the remaining four information sources.

Results

All the five information sources provided recommendations in quantitative terms for the majority of drugs examined in the study (Table 1). AMH provided precise recommendations (N and CI) for the highest number of drugs (n=51), followed by BNF (n=48). Monographs for 44% of the drugs (n=27) were missing from DPRF. However, DPRF generally provided the clearest information for the other drugs. The first analysis showed only slight agreement (K: 0.3) among the five information sources. A moderate agreement (K: 0.4) was observed in the second analysis when the DPRF was excluded. When assessing the individual categories of

drugs, the least agreement was found among the recommendations for gliptins (K: -0.19), followed by genitourinary drugs (K: -0.05), ACE inhibitors (K: -0.03), oral hypoglycaemics (metformin, glimepiride, glibenclamide) (K: 0.04), musculoskeletal drugs (K: 0.15), psychotropic drugs (K: 0.19) and neurological drugs (K: 0.19).

There was marked variation among the information sources in how they presented the contraindicated drugs. In various instances, drugs marked as contraindicated in one source were not mentioned as such in others (Table 2). AHFS recommended avoiding metformin use even in mild renal impairment. However, the avoidance range for metformin according to AMH was CrCl < 30 mL/min, for MIMS it was CrCl < 60 mL/min, for BNF it was eGFR < 30 mL/min and for DPRF it was GFR < 10 mL/min. AMH and AHFS considered glibenclamide to be contraindicated in renal impairment, while DPRF recommended using normal dose in even severe renal impairment (GFR < 10 mL/min). AMH considered codeine as contraindicated, whereas three information source (MIMS, AHFS and BNF) did not specify this contraindication and, interestingly, DPRF recommended using half of the normal dose even if GFR < 10 ml/min. Similarly, drugs that required no adjustment according to one source had explicit quantitative recommendations in other sources. There were seven such instances for six different drugs. Three drugs (candesartan, alprazolam, hydromorphone) for which DPRF recommended no adjustment required were categorised by other sources as requiring it. For vardenafil, the BNF recommended reduced dosage in patients with renal impairment, whereas MIMS and AHFS recommended that no dosage adjustment was required. While MIMS recommended no adjustment for teriparatide, AMH and BNF provided quantitative recommendations. Monographs for both vardenafil and teriparatide were missing from DPRF.

Apart from the dissimilarity in the categories of recommendation, disparity was found among the information sources in how they provided the quantitative recommendation. The dose

reduction and dosing frequency advised for the particular drugs in the varying severities of renal impairment contrasted among the sources (Table 3). On examining the individual information sources, it was found that some of the recommendations were contradictory. For instance, with regard to famotidine in AHFS, this information source suggested using one-half the normal dosage or prolonging the dosing interval to 36–48 hours according to the patient's clinical response in moderate renal impairment (CrCl < 50 ml/min) or severe impairment (CrCl < 10 ml/min). On the other hand, the same information source advised to use one-half the usual adult dosage in adults with CrCl of 30–60 mL/minute/1.48 m^2 of body surface area and use one-fourth the usual adult dosage in patients with CrCl <30 mL/min/1.48 m^2. Other examples were: metoclopramide in BNF, "avoid or use small dose in severe renal impairment"; and bisoprolol in MIMS, "no dosage adjustment is required in patients with impairment of the kidney due to excretion equally by both liver and kidney. Nevertheless, caution is advised" (Table 4).

CrCl was the most common index to direct the dosage adjustment in the information sources. AMH and DPRF recommended dose adjustment based on CrCl calculated by the CG formula. However, BNF provided recommendations based on eGFR calculated by the Modification of Diet in Renal Disease (MDRD) formula.[31] The renal function quantification methods varied among the drug monographs within AHFS and MIMS. For the majority of drugs, dosage adjustment was based on the CG formula and for some drugs the MDRD formula was used, especially when referring to manufacturers' recommendations.

The definition and classification of renal impairment differed in all five sources. The classification for renal impairment in BNF categorised the renal function into five different stages; this complies with the definitions by the British Renal Association.[32] AMH had its own system of classification of renal impairment designed solely to aid the drug dosage adjustment; this differs from the *Caring Australians with Renal Impairment* (CARI)

guidelines.[33] DPRF defined renal impairment based on absolute GFR and divided them into three categories; this does not correspond to any standard classification system. MIMS and AHFS did not provide clear definitions of categories of renal impairment, and terms like mild, moderate and severe impairment were used without definition. Furthermore, various terms were used for dosage recommendation in the information sources without proper definition; these included a clinically significant degree of renal impairment, rapidly deteriorating renal function, and substantial impairment of renal excretory function.

Discussion

There was considerable variation between the information sources in recommendations for the use and dosing of drugs in patients with renal impairment. Vidal et al similarly concluded that there was poor consistency among four information sources: BNF, Martindale, AHFS and DPRF for the renal dosing of 100 drugs used commonly in the hospital setting.[19] However, their study had some limitations, particularly relating to the method of selecting the most commonly prescribed drugs within a hospital environment, rather than focusing on high risk drugs excreted primarily via the renal route.[34,35] Therefore, we compared the drug information sources based on their dosing recommendations for the drugs which have most potential for inappropriate prescribing in kidney disease.

The results of our study illustrate that there is a lack of quantitative recommendations in the various information sources to reliably guide health professionals on appropriate prescribing to minimise adverse outcomes in patients with renal impairment. It is recognised that it is unrealistic to quantify the appropriate dose for some drugs with large pharmacodynamic variability - for instance, ACE inhibitors and β-blockers, whose dosage adjustment should not be based solely on pharmacokinetic parameters but clinical factors like blood pressure and

heart rate as well. However, clear quantitative information in one source and unclear information in other information sources, such as 'increase dosing interval' or 'seek specialist advice in severe impairment', will complicate the prescribing decision.

One of the reasons for the lack of robust dosing information could be the paucity of large population-based studies on dose adjustment in renal impairment. Another contributing factor could be the practice of the drug regulatory authorities, that focuses mainly on clinical trials determining the maximum tolerated dosage in healthy, young individuals.[35] Keeping aside the fact that few studies are available that determine the correct dose in renal impairment, the dissimilarity between standard information sources regarding the reported availability of clinical study data was remarkable; drugs for which one information source mentioned a lack of clinical study data on dose adjustment, other sources provided clear quantitative recommendations.

It is well understood that contraindications and cautions are seldom absolute but the differing recommendations create ambiguity and uncertainty, and can misdirect the users or prescribers. For particular drugs, such as oral hypoglycaemics, H_2 receptor blockers, metoclopramide and many cardiovascular drugs, the information sources often did not provide explicit information for dosage adjustment yet studies have shown that incorrect dosage adjustments are common with these categories of drugs.[17,36] Guidelines for dose adjustment in renal impairment, even for drugs with a narrow therapeutic index (e.g. digoxin and lithium), were poorly mentioned in the information sources. Instead of a clear quantitative recommendation, qualitative and ambiguous terms like "reduce the dose" and "loading dose should be conservative" were often used.

It was found that the information sources were relatively consistent in providing recommendations for newer drugs, such as levetiracetam, memantine, paliperidone,

pramipexole and pregabalin. This improved consistency could be due to the manufacturers providing more robust data for clinical use and dosage adjustment, and regulatory authorities demanding more consistent information. Clearly, regular updating of the drug information sources is necessary, along with a need for all drugs that are to be used in patients with renal dysfunction to undergo at least one pharmacokinetic study in patients with varying degrees of renal impairment prior to marketing. An emphasis should be placed on conducting and disseminating research work focused on determining the correct drug dosage based on renal function.

Uniformity in the categorisation of renal impairment would be desirable as prescribers tend to refer to more than one information source for advice on drug dose adjustment in renal impairment.[37] Keeping in mind the new practice of automatic eGFR reporting, drug dosage recommendations based only on CrCl could be inconvenient.[38,39] Recently, it was suggested that the method of calculating eGFR should be changed to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and that all laboratories should report eGFR values as a precise figure to at least 90mL/min/1.73m^2.[40] However, it has been recommended that the dosage adjustment for drugs with a narrow therapeutic index or excreted primarily by kidney should be guided by CrCl calculated by the CG equation.[41] Further, in elderly or frail patients and in those with a low body mass index, CrCl is the preferred renal function quantification method.[42] Therefore, recommendations for dose adjustment based on both CrCl and eGFR/CKD-EPI would be ideal.

Editors of secondary sources accept the difficulties in finding and compiling the relevant information for patients with renal disease on which clear dosing guidelines can be formulated.[35,44,45] Furthermore, the value of the product information will always be limited by the regulatory process (data requirements, economics, and approval delays) and the generally conservative approach by manufacturers (fear of litigation). It will always be necessary to

interpret the product information and make a risk-benefit decision for individual patients. Also, while adjusting the dose in clinical practice, the prescriber needs to be confident that the pharmacokinetic parameters of the patient they are treating do not vastly differ from the population in which the renal pharmacokinetic study was undertaken.

Our study was limited to drugs used commonly in the community setting, and so excluded renally important drugs used primarily in hospital settings (e.g. aminoglycoside antibiotics). However, in light of the inconsistency in the recommendations for the 61 drugs in our study, we believe a similar result would be obtained if a greater number of renally problematic drugs were examined. Also, we acknowledge that there are other sources of drug dosing information in renal disease that might be used in practice, especially within specialist renal units. However, we have examined the information sources most commonly used by Australian general practitioners and pharmacists in the community setting.

Conclusion

There should be an evidence-based approach to drug dosage adjustment in renal disease to bring uniformity to the recommendations. Further, it would be beneficial to standardise the renal function quantification methods in the drug information sources. We believe that this would reduce the possibility of inappropriate dosing for patients with renal impairment.

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Table 1. Category of dosage recommendations for 61 drugs according to five information sources

Category	**AMH**	**MIMS**	**BNF**	**AHFS**	**DPRF**
Contraindicated (CI)	3	1	1	2	0
Missing (M)	0	0	1	6	27
Numeric (N)	48	41	47	37	30
Non-Numeric (NN)	9	17	12	14	0
No advice (X)	1	0	0	1	0
Not required (Y)	0	2	0	1	4
Total drugs	**61**	**61**	**61**	**61**	**61**

Table 2. Discrepancies among the information sources on how they presented contraindicated drugs and the drugs that do not require dose adjustment

Drugs	AMH	MIMS	BNF	AHFS	DPRF
Glibenclamide	CI	NN	NN	CI	N
Codeine	CI	NN	NN	NN	N
Metformin	N	N	N	CI	N
Vardenafil	X	Y	N	Y	M
Candesartan	N	N	N	NN	Y
Alprazolam	NN	NN	NN	NN	Y
Bupropion	NN	NN	N	NN	Y
Hydromorphone	NN	NN	NN	NN	Y
Teriparatide	N	Y	N	X	M

CI: Contraindicated, M: Missing , N: Numeric, NN: Non-Numeric, X: No advice mentioned, Y:Dosage adjustment not required

Table 3. Some examples of discrepancies in quantitative recommendations among the information sources

Drugs/dose for normal renal function	AMH		MIMS		BNF		AHFS		DRIRF	
	CrCl (mL/min)	***Dose (Max/day***	***CrCl (mL/min)***	***Dose (Max/day)***	***eGFR (mL/min/1.73 m^2)***	***Dose (Max/day)***	***CrCl (mL/min)***	***Dose (Max/day)***	***GFR (mL/min)***	***Dose (Max/day)***
Metformin 500-850 mg bd	60-90	2 g	<60	Avoid	<45	Dose should be reviewed	Avoid in RI		>50	50
	30-60	1 g			<30	Avoid			10-50	25%
	<30	Avoid							<10	Avoid
Glibenclamide 1.25-20 mg q24h	RI	Avoid	Severe RI	Avoid	Use with care in mild to moderate RI Avoid where possible in severe RI		RI	Avoid	>50	No data
									10-50	No data
									<10	100%
Sitagliptin 100 mg OD	30-50	50 mg	<60	Avoid	30-50	50 mg	30-50	50 mg	NA	
	<30	25 mg			<30	25 mg	<30	25 mg		
Saxagliptin 5 mg OD	<50	2.5 mg	>50	5 mg	2.5 mg in moderate to severe RI; use with caution in severe RI		>50	NR	NA	
			30-50	Avoid			≤50	2.5 mg		
			<30	Avoid			<30	Avoid		
Teriparatide 20 micrograms OD	<30	Avoid	Dosage adjustment not required		Caution in moderate impairment; avoid if severe RI		No advice for dosage adjustment in RI		NA	

Colchicine Acute 2 mg, then 0.5 mg q6h chronic:0.5-1 mg q24h	<30	Increase dose interval	Avoid in severe RI		10-50	Reduce dose or increase dose interval	<30	0.3 g daily	>50	100%
	<80	Avoid in acute attack			<10	Avoid			10-50	50-100%
									<10	25%
Bupropion 150-300 mg OD	RI: 150 mg		Use reduced dose and/or frequency		RI: 150 mg		Use with caution in RI		No need for dosage adjustment	
Duloxetine 30-60 mg OD	<30	30 mg OD	<30	30 mg	<30	Avoid	<30	Avoid	NA	
Note: RI: Renal impairment, ID: Initial Dose, MD: Maintenance Dose, ND: Normal Dose, NA: Not available, NR: Not required										

Drugs	AMH	MIMS	BNF	AHFS
Analgesics	**Morphine**: Use an alternative opioid (or reduce dose if CrCl <50 mL/minute). **Hydromorphone:** Reduce dose in renal impairment and monitor for adverse effects.	**Tramadol:** Avoid use or reduce dose. **Codeine**: Use with caution. **Oxycodone**: Dosage should be reduced and adjusted according to the clinical situation.	**Morphine**: Avoid use or reduce dose. **Codeine**: Avoid use or reduce dose. **Hydromorphone:** Avoid use or reduce dose.	**Morphine:** Use with caution. **Codeine**: Care should be exercised. **Hydromorphone:** Reduce initial dose. **Oxycodone**: Reduce dose and adjust according to the clinical situation.
Neurological	**Baclofen:** 5 mg initially; titrate dose cautiously according to response. **Topiramate**: Reduce maintenance dose. **Levetiracetam**: Reduce dose in renal impairment.	**Topiramate**: Renal clearance is decreased in renal impairment.	**Topiramate**: Use with caution if eGFR less than 60 mL/minute/1.73 m^2.	**Baclofen:** May be necessary to reduce either oral or intrathecal dosage in renal impairment.
Psychotropic	**Lithium:** Use reduced dose and monitor carefully. **Bupropion**: Use low dose and monitor for adverse effects. **Benzodiazepines**: Use a lower initial dose in severe impairment.	**Lithium:** Avoid in severe renal impairment.	**Lithium**: Avoid if possible or reduce dose. **Bupropion**: Reduce dose to 150 mg daily in renal impairment.	**Lithium:** Should not be used in patients with severe renal disease. **Bupropion:** Use with caution in patients with renal impairment. ***Venlafaxine**: Reduce dose by 25–50% in patients with mild-to-moderate renal impairment and by 50% in HD.
Blood disorders	**Enoxaparin**: Use with caution in renal impairment	_	**Enoxaparin:** Reduce dose consult product literature.	_

	reduce dose if CrCl <30 mL/minute.			
Musculo-skeletal	–	**Methotrexate**: Avoid in severe renal impairment. ***Strontium ranelate**: No dosage adjustment in patients with mild to moderate renal impairment. Avoid in severe impairment.	–	**Methotrexate**: Particular attention to close monitoring is recommended.
Cardio-vascular	**Sotalol**: Increase dosing interval. Seek specialist advice for dose adjustment in severe impairment. **Bisoprolol**: No dose reduction required up to 10 mg daily in renal impairment	**Digoxin**: Use with caution in renal impairment. **Captopril**: Initial daily dosage should be reduced **Bisoprolol**: No dosage adjustment is normally required up to the max dose of 10 mg.	**Digoxin**: Reduce dose and monitor plasma-digoxin concentration.	***Candesartan**: 4 or 8 mg daily in severe impairment. **Digoxin**: Loading doses should be conservative. **Spironolactone**: Use with caution in renal impairment, contraindicated in rapidly deteriorating renal function, substantial impairment of renal excretory function.
Endocrine	–	–	**Glimepiride**: Should be used with care. **Glibenclamide:** Should be used with care.	**Glimepiride**: Initial dosing should be conservative.
Gastro-intestinal	–	**Metoclopramide**: Initiate therapy at half of the dose in patients with clinically significant degrees of renal impairment. **Ranitidine**: Reduce dose on severe renal impairment.	**Metoclopramide**: Avoid or use small dose in severe impairment.	–

* Mild, moderate and severe impairment were not defined in the information sources.

Appendix 1: Drug list used in the study

Medicines that may accumulate and require renal function monitoring				
Analgesics	**Genitourinary**	**Blood**	**Endocrine**	**Musculoskeletal**
Codeine	Solifenacin	Dabigatran	Glibenclamide	Allopurinol
Hydromorphone	Sildenafil	Enoxaparin	Glimepiride	Bisphosphonates
Morphine	Tadalafil	Rivaroxaban	Saxagliptin	Colchicine
Oxycodone	Tolterodine		Vildagliptin	Strontium ranelate
Tramadol	Vardenafil		Sitagliptin	Teriparatide
			Metformin	

Neurological	**Psychotropic**	**Cardiovascular**	**Gastrointestinal**
Baclofen	Acamprosate	ACE-inhibitors	H2-antagonists
Gabapentin	Amisulpride	Angiotensin receptor blockers	
Galantamine	Benzodiazepines	Atenolol	
Levetiracetam	Bupropion	Bisoprolol	
Memantine	Desvenlafaxine	Digoxin	
Methysergide	Duloxetine	Fenofibrate	
Paliperidone	Lithium	Spironolactone	
Pramipexole	Reboxetine		
Pregabalin	Venlafaxine		
Topiramate			
Varenicline			

Source:www.veteransmates.net.au