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THE IMPACT OF GUIDANCE ON CITALOPRAM'S EFFECTS ON THE QT PERIOD ON THE PRACTICE OF CLINICIANS

James Austin[1,2], Keonwoo Yi[1,3] , Mark Agius[2,4,5] & Rashid Zaman[4,5]

[1]*School of Clinical Medicine University of Cambridge, Cambridge, UK*
[2] *Clare College Cambridge, The University of Cambridge, Cambridge, UK*
[3]*Downing College Cambridge, Cambridge, UK*
[4]*Department of Psychiatry, University of Cambridge, Cambridge, UK*
[5]*South Essex Partnership University Foundation Trust, UK*

SUMMARY

In 2011, the FDA published guidelines regarding the prescribing of citalopram and escitalopram following publication of evidence showing prolongation of the QT period at therapeutic doses. This paper looked at the impact of these guidelines on the prescribing practices of clinicians in one centre. It showed that clinicians have changed practices in accordance with the guidelines for citalopram but no clear patterns were seen in escitalopram or when looking individually at thespecific guidelines for patients over 60 years of age. There was no evidence of increased concordance by clinicians with the guidelines in patients taking other QT prolonging drugs who are at additional risk. Overall, the guidelines have made an impact on practice but this is partial and2% of all patients still remain on regimes that do not fit the guidelines. The possible reasons for this are explored.

Key words: *citalopram – escitalopram - QT interval – QTc - clinicians – prescribing – practices – guidelines – guidance – recommendations - SSRI*

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INTRODUCTION

The existence of psychotropic substances has been known for a long time but their therapeutic potential has only become realised in the last half century leaving psychopharmacology relatively junior as a field in medical research. Subsequently, most drugs used in psychiatry carry a large burden of side effects.

One sideeffect is the prolongation of the QT interval.

The QT interval measures the time between the start of the Q wave and the end of the T wave in electrical cycle of the heart. It represents electrical depolarization and repolarization of the ventricles. A long QT interval is a marker for the pssibility of ventricular tachyarrhythmias such as torsades de pointes and thus a marker of the risk of sudden death.

The QT interval depends on the heart rate and can be adjusted to improve the detection of patients who are at increased risk of ventricular arrhythmia.This corrected QT is referred to as QTc.The correction is made using Bazett's formula (Bazett 19200)

This side effect is seen with multiple classes of drugs andcan beeasily overlooked in clinical practice. However it carries the risk of generating a Torsades de pointes (TdP) ventricular arrhythmia which can progress to ventricular fibrillation particularly if an individual undergoes stress, fear or physical exertion.

Many drugs have been implicated in causing an acquired long QT interval. These include antipsychotics, tricyclic antidepressants (TCA) and more recently the serotonin-specific reuptake inhibitors (SSRIs) (Table 1).

Table 1. NICE guidance on maximum prescribed doses for citalopram and escitalopram. Following FDA recommendations

Population group	Maximum Dose	
	Citalopram	Escitalopram
Adults	40mg	20mg
Over 65 year olds	20mg	10mg
Hepatic impairment	20mg	10mg

The first evidence of SSRIs causing QT prolongation was seen in SSRI overdose studies of which only citalopram overdoses featured aQTc length longer than 450ms (Isbister 2004). Follow up studies with escitalopram, the S-enantiomer of citalopram, showed that 14% of overdose patients had an abnormally long QT interval which matched that seen with citalopram (Van Gorp 2009). The discovery that therapeutic doses could prolong the QT interval was first reported by the FDA in 2011 (FDA 2011). Citalopram caused QTprolongation of 8.5 and 18.5ms at 20mg and 60mg doses respectively. Concomitant results were found in escitalopram where a 30mg dose prolonged the QTc by 10.7ms.

Following this, the FDA published new guidance reducing the maximum dose of citalopram from 60mg to 40mg in adults and to 20mg in people over 60 years of age and with hepatic impairment. Further recommendations emphasised greater caution on prescribing to people with cardiac impairments, metabolic disturbances or taking medications that increase the risk of TdP. In these patients, regular ECG monitoring should be undertaken and any prescription of citalopram should be stopped if the QTc was greater than 500ms.

In the UK, NICE have published similar guidance with minor modifications. The FDA recommendations for over 60 year olds were changed to over 65 year olds by NICE. Corresponding changes were made for escitalopram. The maximum dose of 20mg remained unchanged but forpatients over 65 years old or with hepatic impairment, the dose was reduced to 10mg (MHPRA 2011).

Further research has provided mixed results. A large study of ECGs showed a dose dependent increase in QTc for citalopram and escitalopram but not for other SSRIs (Castro 2013). Looking across studies, a systematic review (Funk 2013) showed that at therapeutic doses, citalopram and escitalopram are the only SSRIs to have a significant effect on QTc and this is supported by a metanalysis (Beach 2014) which showed citalopram to have a greater effect on QTc than other SSRIs. However a study of elderly surgical patients preanaesthesia ECGs showed no difference in QT interval for patients on SSRIs even when looking individually at citalopram (van Haelst 2014).

As a whole the evidence shows that SSRIs cause some prolongation of the QT interval and of these, citalopram and escitalopram have the largest effect. However, we still know little about QT prolongation, in particular the mechanisms causing it and the effects of QT prolonging drugs in combination.

The FDA guidance has generated an increase in research into the SSRIs but as with all guidance, its end result should lie in informing and steering clinical decisions. This study aims to look at whether clinicians have changed their practice in accordance with the FDA recommendations. It also looks at prescribing practices in patients who are taking citalopram or escitalopram with other QT prolonging drugs for which the NICE guidance recommends that this be avoided.

METHODS

Data was sourced from the database of the Bedford East CMHT team which represents one consultant, two associate specialists and a registrar.The database is updated annually in August and the 2010 and 2013 datasets were chosen for analysis.There were 1060 patients in the 2010 dataset and 1265 in the 2013 dataset. Patients were excluded from analysis if they were under 18 years old or were recorded as deceased in either dataset. Patient ages were taken as of the 1st of August for each of the datasets of the respective year.

RESULTS

In 2010, there were 193 patients prescribed citalopram or escitalopram of which 18 were over 60 years old and 102 were on other QT prolonging drugs. In 2013, 191 patients were prescribed citalopram or escitalopram of which 23 were over 60 years old and 97 were on other QT prolonging drugs.Drugs included as prolonging the QT period were antipsychotics, TCAs, venlafaxine and lithium (Table 2).

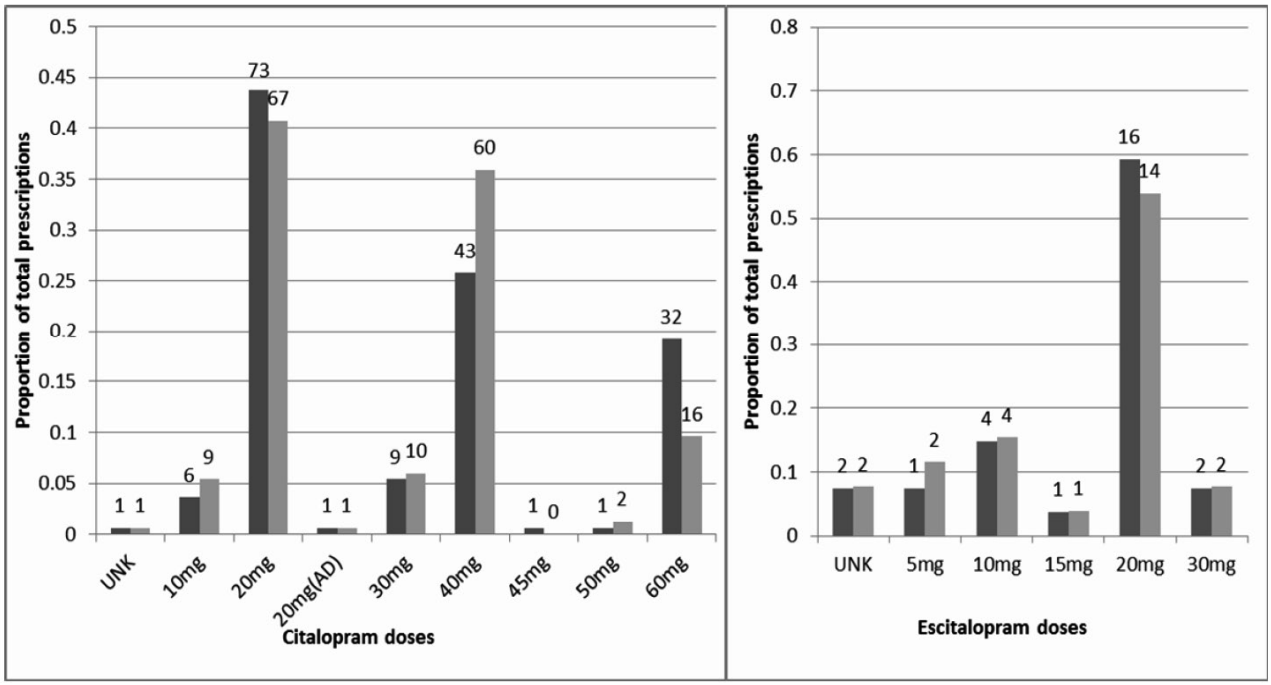
There were two less patients in 2013 on citalopram or escitalopram and 5 less patients in 2013 on a combination with another QT prolonging drug. There were 5 more patients over the age of 60 in 2013 and this reflects bothdataset cohorts having a similar distribution of dates of births. There appear to be no macroscopic changes in the number of patients taking citalopram and escitalopram or the number taking these with another QT prolonging drug.

The doses prescribed for all patients areshown in Figure 1. The main change is a halving of citalopram 60mg prescriptions from 32 to 16. This co-occurs with a rise in the number of 40mg prescriptions. There are changes for other doses but these are small. This suggests that doctors have reduced 60mg prescriptions in conjunction with the guidelines. In escitalopram, the guidance did not change the maximum recommended dose and it remained at 20mg. There are two prescriptions of 30mg which remain in both datasets. There is a small reduction in 20mg doses from 16 to 14 patients but the dataset is small and no clear patterns can be deduced.

A similar picture is seen in Figure 2 with patients on another QT prolonging drug. In citalopram, there is a similar halving ofthe number of 60mg doses with a correspondingrise in 40mg doses. In escitalopram, there is again a small reduction in 20mg doses from 8 to 5 patients (Table 3).

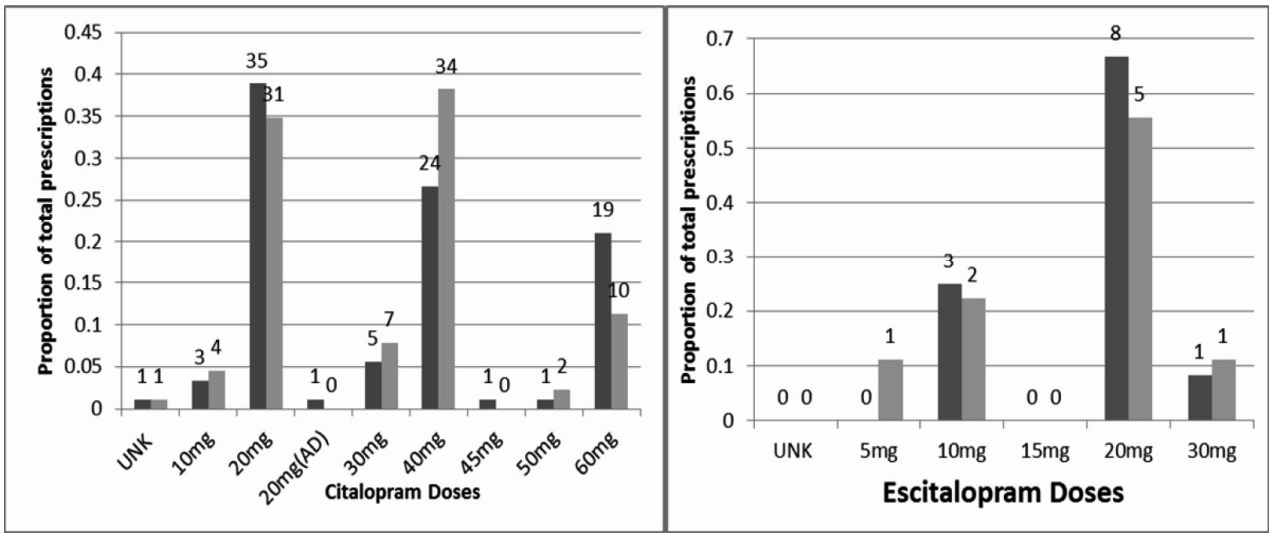
Table 2. Records of the number of patients taking citalopram or escitalopram and within this group, those specifically over 60 years old and those prescribed another QT prolonging drug

		2010 data	2013 data
All patients	Citalopram + Escitalopram	193	191
	Citalopram only	167	166
	Escitalopram only	26	25
Patients over 60 years old	Citalopram + Escitalopram	18	23
	Citalopram only	13	16
	Escitalopram only	5	7
In combination with other QT prolonging drug(s)	Citalopram + Escitalopram	102	97
	Citalopram only	90	88
	Escitalopram only	12	9



20mg (AD) = 20mg taken on alternate days; UNK = unknown dose

Figure 1. Bar chart showing the frequency of different doses as a proportion of the total number of prescriptions for the respective drug. Darker bars represent 2010 data and paler bars represent 2013 data. Numbers above the bar show the actual number of prescriptions for that dose



20mg (AD) = 20mg taken on alternate days; UNK = unknown dose

Figure 2. Bar chart containing data for patients who are taking another QT prolonging drug

Table 3. Data showing the number of prescriptions of doses within and outside the FDA recommendations. A chi-squared test was performed on citalopram data and Fisher's exact test was performed on escitalopram data

	2010 data	2013 data	
Citalopram			
40mg or less	132	147	χ^2=9.28
More than 40mg	34	18	p=0.002**
Escitalopram			
20mg or less	22	21	
More than 20mg	2	2	p=1.0

By grouping the doses into those exceeding and those within the recommendations, there is a statistically significant change with more citalopram prescriptions meeting the recommended doses in 2013 than 2010. No change is seen with escitalopram which reflects the two patients who remained above the recommended doses in both datasets (Table 4).

The analyses shows that while there has been no large scale change in the number of citalopram or escitalopram prescriptions, there has been a response by clinicians in response to the guidelines to adjust the drug doses. There is no clear difference seen with patients taking other QT prolonging drugs suggesting that clinicians have not been able to focus their attempts to meet the recommendations on these patients who are at additional risk.

The FDA and NICE specify separate maximum doses for older adults but give different age ranges. In the over 60 year old patients on citalopram, there is an almost significant result with an increasing proportion of patients being on recommended doses in 2013 than 2010. This is not however reflected in the over 65 year old patients.Conversely for escitalopram, in both over 60 and 65 year old patients, there is an increase in the proportion of prescriptions exceeding the recommendations in 2013. None of these changes are significant and this again reflects the small sample sizes.

The results show that there has been some change in that clinicians are following the guidelines by altering their prescribing practices and this maybe be occurring in two possible ways. Firstly, clinicians may be changing prescribing practices in new patients who join the service or clinicians could be altering the prescriptions of patients known to the service before the guidance was published (Figure 3).

To investigate this, all patients on non-recommended doses were studied across both datasets. In the 2010 dataset before the guidance, there were 190 patients with a recorded dose of citalopram or escitalopram. Of these, 23% (MHPRA 2011) were on a dose above what the future recommendations would be.

Between 2010 and 2013, 41 new patients joined the service andwere prescribed citalopram or escitalopram of which 9.8% (MHPRA 2011) were placed on a dose above the recommendations. Therefore in new patients, a smaller proportion was on a dose exceeding the maximum recommended dose than patients in 2010.

Of the 190 patients in 2010, 147 remained on citalopram or escitalopram in 2013 and 14% (20) of these remained on a dose above the recommendations by 2013. Therefore a smaller proportion of the patients who remained with the service in 2013 were on a non-recommended dose than the patients in 2010.

Table 4. Data for patients over 60 years of age and over 65 years of age reflecting the FDA and NICE guidance respectively showing the number of prescriptions for doses within and outside the guidelines. Fisher's exact tests performed

	Over 60 years of age (FDA)			Over 65 years of age (NICE)		
	2010 data	2013 data		2010 data	2013 data	
Citalopram						
20mg or less	2	8		0	2	
More than 20mg	11	8	p=0.11	3	7	p=1.0
Escitalopram						
10mg or less	2	2		2	1	
More than 10mg	2	4	p=1.0	0	2	p=0.40

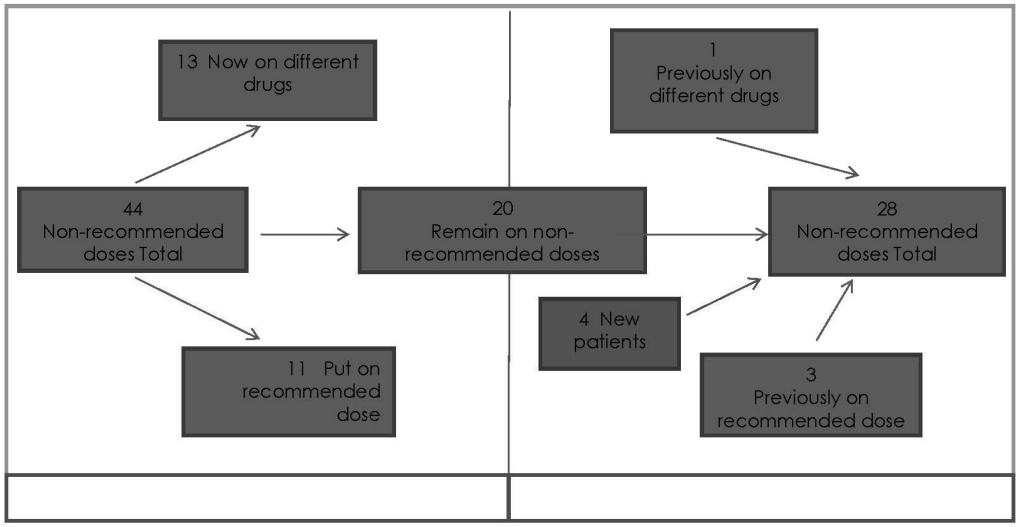


Figure 3. Diagram shows the number of patients from 2010 and 2013 on doses that are not within the recommendations and their status in the corresponding dataset. Note that 'New patients' have no entry in the 2010 dataset as they were not known to the services

Together, the results show that clinicians have managed to meet the recommendations in both new patients and those already known to the service.

In addition to changing drug doses, doctors can also change the drug prescribed. Of the patients on non-recommended doses of citalopram or escitalopram in 2010, 8 were changed to an alternate SSRI and 5 to a non-SSRI drug by 2013 while only 1 patient was transferred from another drug in 2010 to a non-recommended dose of citalopram in 2013.

DISCUSSION

The study provides useful insights but also has drawbacks of which the main one is the small sample size available. This limits the degree to which patterns in the data can be detected and because only 4 clinicians' prescribing practices are represented here, the data can be easily distorted by individual practices. Likewise, the data is all from one centre. Prescribing practices may differ more between centres. Information from other centres would show if the effects seen here are widespread and would also give more statistical power allowing better analysis of subgroups within the cohort.

In essence, the results show that the FDA guidance has made an impact. Clinicians still prescribe citalopram but have reduced the number of high dose prescriptions. It is less clear if the guidelines in older adults have been met. The reductions while present are only partial and there remain 28 patients in 2013 on doses above the recommendations for their age. This is 2% of all Bedford East CMHT patients and there are several possible reasons for this.

The first is that clinicians have not been able to completely follow the guidelines. This is understandable given time pressures on clinician consultations and patients not always attending their appointments. Alternatively, the patient could refuse to have their treatment altered particularly if they have found the regime very helpful. In a few patients, it may also be considered generally less risky to keep the dose unchanged. These represent patients at very high risk to themselves or others and in which their stable management has only been achieved by a carefully titrated drug regime. In these cases, it may be safer to keep the regime unchanged in order to maintain this even if there is the risk of a prolonged QT period.The latter two reasons while compelling should not deter the clinician from meeting the guidelines for the FDA stated that no additional benefits are conferred by placing a patient on a higher dose of citalopram than 40mg (FDA 2011).

A final reason that may account for the incomplete compliance with the guidelines is that many patients who have been managed on psychiatric medications for a long time already receive routine ECG monitoring and if the QT period is normal and has been stable over time then the clinician may see no reason to change the dose prescribed.

There are further areas that could be explored with this data. The patients on citalopram and escitalopram have a range of diagnoses which each require different clinical considerations and different drug regimens. Likewise there are additional factors that influence prescribing which were not investigated here. ECGs with recorded QT periods, past cardiac disease and non-psychiatric medications are all factors that can alter clinicians prescribing practices and werenot available in this study.

Looking forward, this study illustrates how clinical practice moves forward and improves. From suggestions of QT prolongation in SSRIs ten years ago to the publication of evidence and guidance three years ago, we see that clinicians have clearly made a response to guidance and that all the research in this field has now yielded clear quantifiable change. However we must contrast this with a question as to why the change is only partial and why a minority of patients still remain on doses that could be placing them at risk.

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Correspondence:

James Austin
School of Clinical Medicine University of Cambridge
Cambridge, UK
E-mail: jra46@cam.ac.uk