

Supplementary Material

Dear Doctor Letters regarding Citalopram and Escitalopram: Guidelines vs real world data

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Table 1 Suppl.

Psychotropic drugs: Risk of QTc prolongation and / or of Torsade de pointes (TdP)
According to Wenzel-Seifert et al. 2011, Table in supplementary material

	QTc prolongation	TdP Risk Arizona CERT
Thiorizadine	+++	1
Pimozide	+++	1
Methadone	+++	1
Levomethadone	+++	1
Chlorpromazine	++	1
Haloperidol	+	1
Sertindole	+++	2
Quetiapine	+++	2
Lithium	+++	2
Risperidone	++	2
Clozapine	++	2
Ziprasidone	++	2
Venlafaxine	+	2
Chloralhydrate	+	2
Paliperidone ER	-	2
Amitriptyline	+++	3
Doxepine	+++	3
Imipramine	+++	3
Desipramine	+++	3
Nortriptyline	+++	3
Fluoxetine	++	3
Clomipramine	++	3
Maprotiline	+++	-
Melperone	+++	-
Levomepromazine	++	-
Sulpiride	++	-

QTc prolongation

- + mild (>5 and <9 ms) or only in case of overdose or intoxication (not calculated as risky)
- ++ moderate (≥ 9 and <16ms)
- +++ severe (≥ 17 ms)

TdP risk according to the Arizona CERT

1. generally accepted elevated risk of TdP
 2. rare cases of TdP, possible but not adequately documented TdP risk
 3. weak association with TdP; (not calculated as TdP risk)
- no risk of TdP reported

All psychotropic substances with +++ or ++ in QTc prolongation and/or 1. and 2. in TdP risk were classified as risky drugs.

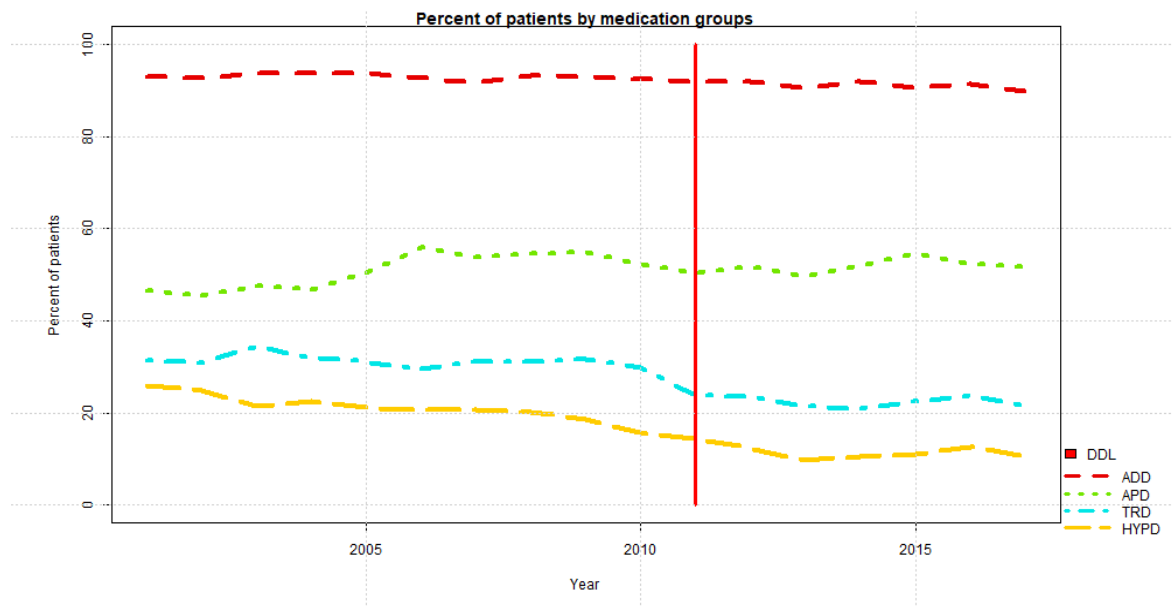
Table 2 Suppl. Study Population (Major Depressive Disorder (MDD), 2001 – 2017, all)

Total number of patients	43,480	-	-
Number of males	16,128	-	37.1%
Number of females	27,352	-	62.9%
Average age males	49.1	SD:	15.5
Average age females	51.6	SD:	16.6
Mild MDD ("F32.0", "F33.0")	497	-	1.1%
Males	206	-	1.3%
Females	291	-	1.1%
Moderate MDD ("F32.1", "F33.1")	11,437	-	26.3%
Males	4,191	-	26.0%
Females	7,246	-	26.5%
Severe MDD ("F32.2", "F33.2")	24,912	-	57.3%
Males	9,207	-	57.1%
Females	15,705	-	57.4%
Severe MDD with psychosis ("F32.3", "F33.3")	5,499	-	12.6%
Males	2,096	-	13.0%
Females	3,403	-	12.4%
Other or no info MDD ("F32", "F32.8", "F32.9", "F33", "F33.4", "F33.8", "F33.9")	1,129	-	2.6%
Males	425	-	2.6%
Females	704	-	2.6%

SD: Standard deviation

The data for the study population was taken from the AMSP dataset with the following constrains: 2001-2017, age ≥ 18 and <90 , diagnosis codes F32- and F33- and at least one prescription of a psychotropic drug.

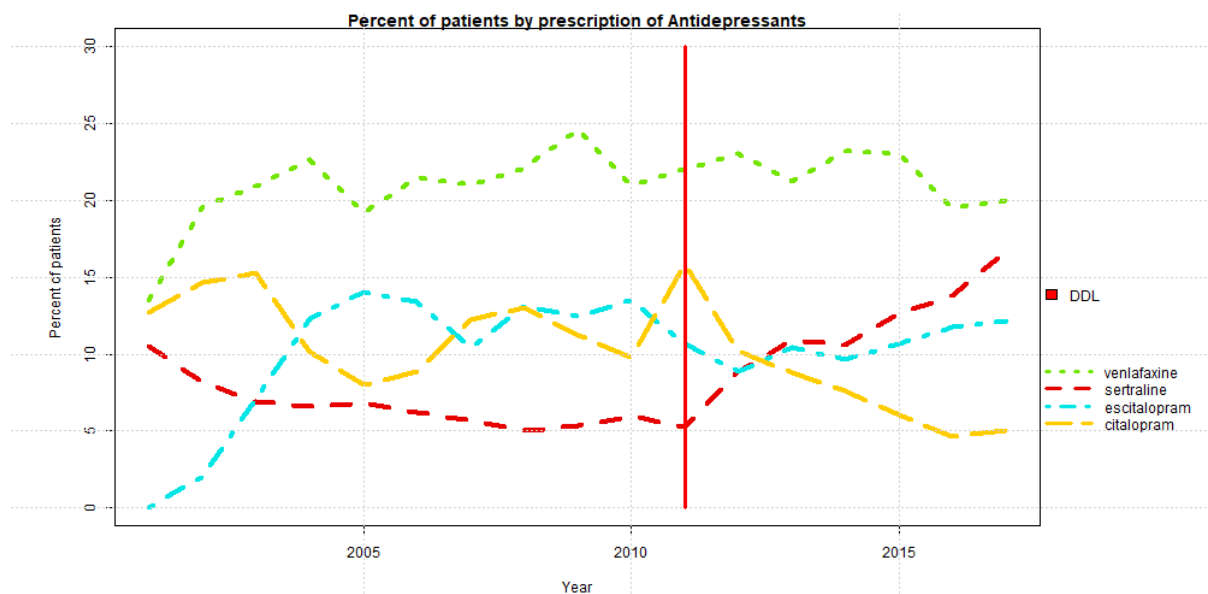
Figure 1 Suppl. Percent of patients treated with the respective psychotropic drug group



Prescription of classes of psychotropic drugs: Antidepressant drugs (ADD), Antipsychotic drugs (APD), Tranquilizing drugs (TRD), Hypnotic drugs (HYPD)

The trends of decreasing prescriptions of TRD and HYPD appear to be unaffected by Dear Doctor Letters (DDL) in 2011; no essential change for ADD and APD.

Figure 2 Suppl. Percent of patients treated with antidepressant drugs

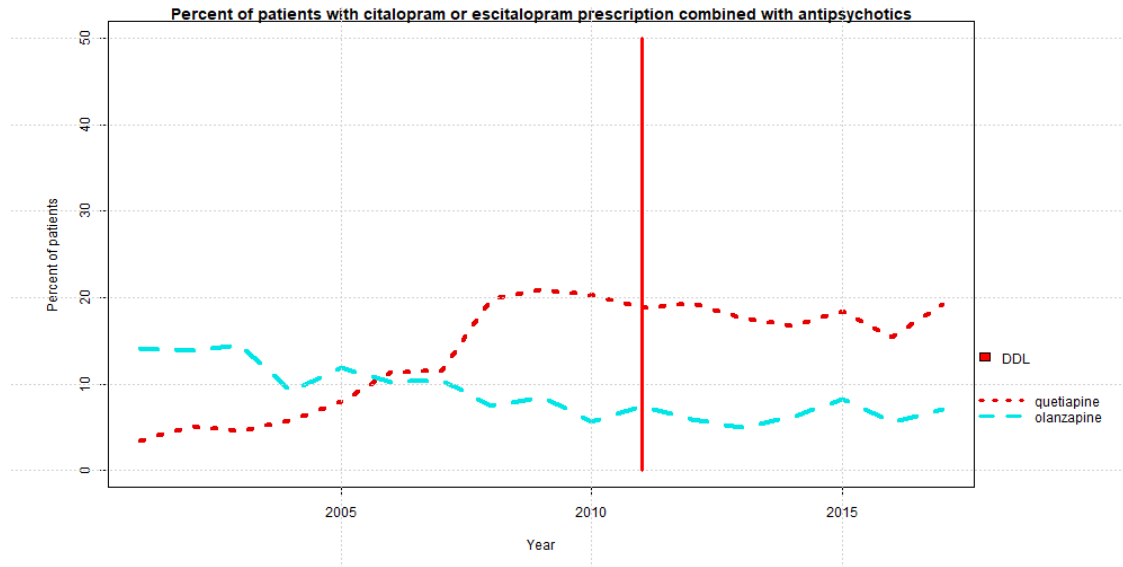


Prescription of citalopram, escitalopram, sertraline and venlafaxine

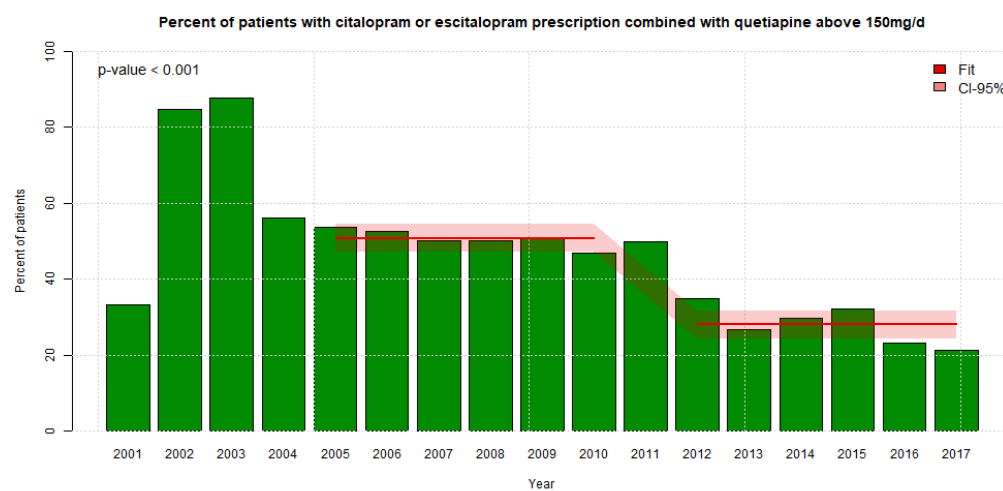
Within the group of ADD there was a decrease of prescriptions of citalopram while sertraline prescriptions increased after DDL in 2011.

Figure 3 Suppl. Combination of es-/citalopram with quetiapine

a)



b)



- a) Percent of patients treated with es-/citalopram combined with quetiapine (n=1097) or olanzapine (n= 600), the two most prescribed combinations of es-/citalopram with antipsychotics.
- b) Percent of patients dosed above 150mg/d of quetiapine in combination with es-/citalopram.

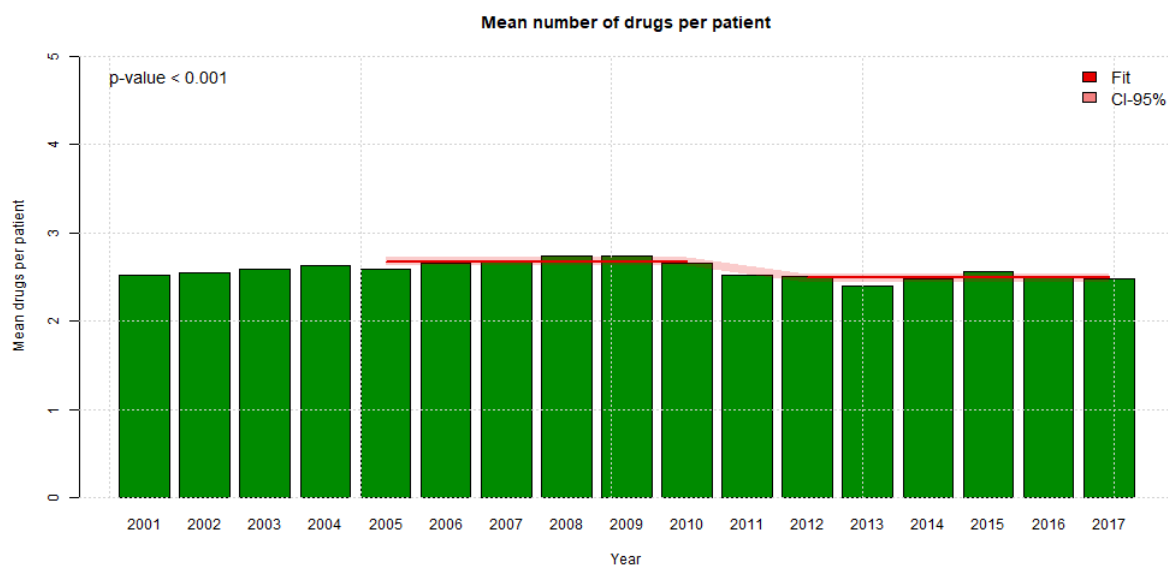
The percentage of combinations of es-/citalopram with quetiapine remained rather stable before and after DDL in 2011 (about 20%; Figure a), but the proportion of “high” dosages of quetiapine (>150mg/d) in combination with es-/citalopram decreased significantly after DDL in 2011 ($p < .001$; Figure b).

The proportion of es-/citalopram patients on quetiapine above 150 mg/d reduced from 51% to 28%; exact values: 50.7% (SE 1.7) to 27.9% (SE 2.3), $p < .001$, comparing six years before and after DDL. Three-year comparison values: 49% to 30%. On the other hand, the proportion of patients dosed 50mg quetiapine or lower increased from 22.3% to 41.8% (six years; three-year comparison 22.4% to 37.6%).

After the DDLs, an increasing proportion of es/citalopram patients in combination with es-/citalopram were treated with low doses of quetiapine (up to 50 mg/d), i.e., doses that are sedative and sleep inducing rather than antidepressant.

Note: The most prescribed antipsychotic drugs in combination with es-/citalopram in the study population were (number of patients, $n \geq 50$): quetiapine (1097), olanzapine (600), risperidone (462), pipamperone (329), promethazine (313), prothipendyl (271), melperone (190), chlorprothixene (181), aripiprazole (164), amisulpride (91), perazine (63), haloperidol (50).

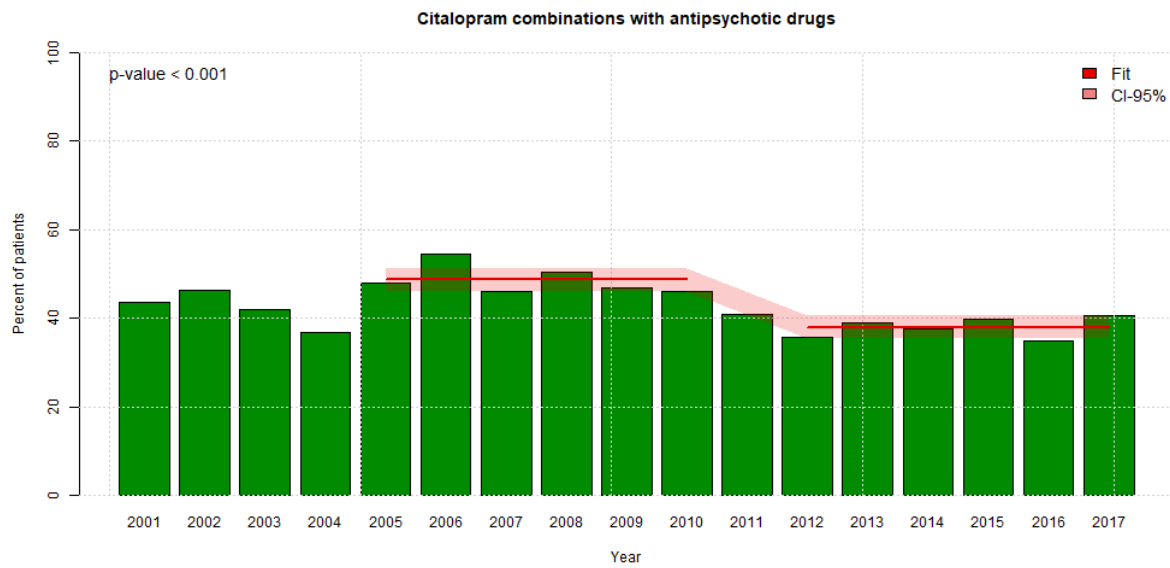
Figure 4 Suppl. Polypharmacy with psychotropic drugs



Mean number of prescribed psychotropic drug per patient: a slight decrease of psychotropic combinations before and after DDL in 2011, yielding a statistically significant result due to low variance ($p < .001$).

The number of concomitant psychotropic medications prescribed decreased from 2.7 (SE 0.02) in 2005-2010 to 2.5 (SE 0.03) in 2012-2017, $p < .001$, when comparing six years before and after the DDL. The three-year comparison showed almost identical results: 2008-2010: 2.7 (SE 0.03) to 2012-2014: 2.5 (SE 0.04)

Figure 5 Suppl. Citalopram combinations with antipsychotic drugs

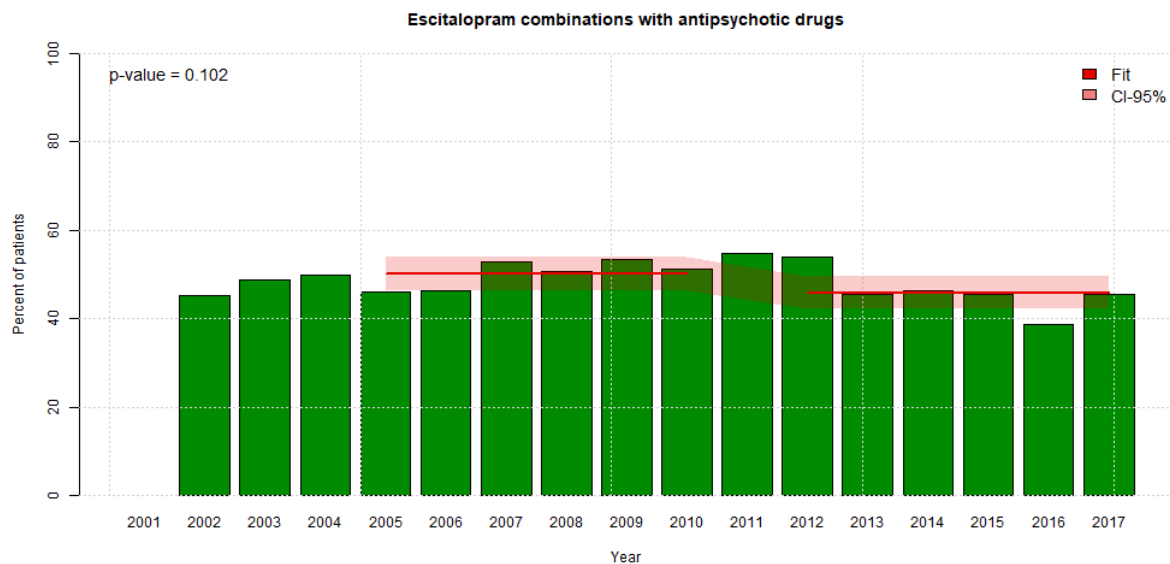


Combinations of escitalopram with APD (in percent)

Statistics 2005-2010 vs 2012-2017: 48.63% versus 37.9%, $p < .001$

(For comparison: 2008-2010 vs 2012-2014: 47.8% versus 37.4% %, $p < .003$)

Figure 6 Suppl. Escitalopram combinations with antipsychotic drugs



Combinations of escitalopram with APD (in percent)

Statistics 2005-2010 vs 2012-2017: 50.1% versus 45.8% (n.s.)

(For comparison: 2008-2010 vs 2012-2014: 51.8% versus 48.5% (n.s))