Urbanisation and neighbourhood deprivation impact chronic pharmacological pain treatment - a large scale longitudinal cohort study in the Netherlands

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Original article

Pain and the City:

Observational evidence supporting contextual effects on persistent pain

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Abstract:

Objective: To examine whether urbanization and neighbourhood deprivation would impact chronic pharmacological pain treatment in terms of greater probability of analgesic escalation, accompanied by increased prescription of psychotropic medication.

Design: Longitudinal analysis of a population-based routine prescription database in the Netherlands.

Setting: Representative sample of pharmacies and dispensing general practitioners, covering 73% of the Dutch nationwide medication consumption in primary care and outpatients.

Participants: 449,410 patients aged 15-85 years were included, of whom 166,374 were in the *Starter group* and 283,036 in the *Continuation group* of chronic analgesic treatment.

Main outcome measure: Escalation of analgesics (i.e. change to a higher level of analgesic potency, classified in five levels) in association with urbanization and dichotomous neighbourhood deprivation was analysed over a six-month observation period.

Results: In both *Starter* and *Continuation* groups, escalation was positively associated with urbanization in a dose response fashion (Starter group: OR (urbanization level 1 compared to level 5): 1.24; 95% CI 1.18 to 1.30; Continuation group: OR 1.19; 95% CI 1.14 to 1.23). A weak but independent association was apparent with neighbourhood deprivation (Starter group: OR 1.06; 95% CI 1.02 to 1.11; Continuation group: OR 1.04; 95% CI 1.01 to 1.08). Use of somatic and particularly psychotropic co-medication was independently associated with escalation in both groups.

Conclusion: Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of an increased rate of psychotropic medication

prescriptions, suggesting pain outcomes are influenced by area influences affecting mental health.

Introduction

The validity of the well-known epidemiological association between urban environment and mental health[1-3] is supported by work showing that urban living is associated with increased amygdala activity[4], a key region in the regulation of stress, affective experience and pain[5 6]. Pain is the natural comorbid mental experience of somatic conditions[7 8]. In turn, pain is strongly influenced by comorbid mental disorders[9 10]. Given evidence of urban impact on risk for mental disorders, including psychiatric medication prescriptions[11], we hypothesized that pain outcomes, indexed through prescriptions, would be poorer in urban environments and disadvantaged urban neighbourhoods. Pain outcomes were examined at the level of primary care and specialist outpatient care and defined in two ways: (i) escalation of analgesic treatment (i.e. prescription of more potent analgesics) and (ii) co-prescription of psychotropic medication in addition to analgesic treatment.

Objective

We examined the hypothesis that chronic pharmacological pain treatment of outpatients and patients in primary care would show escalation of analgesics in association with the level of urbanization and neighbourhood index of deprivation. It was predicted that the highest levels of urbanization and neighbourhood deprivation would be associated with escalation of analgesic treatment to more potent pain medication (e.g. tramadol, morphine, methadone, etc.), while lower levels of urbanization and neighbourhood deprivation would be associated with less potent analgesics (e.g. paracetamol, aspirin, ibuprofen, etc.). Furthermore, we examined the hypothesis that escalation of analgesics would predict prescriptions of psychotropic medication (e.g. antidepressants, antipsychotics, mood

stabilizers, etc.) in patients prescribed chronic analgesic treatment. Study hypotheses were specified before inspection of the data.

Method

Data collection

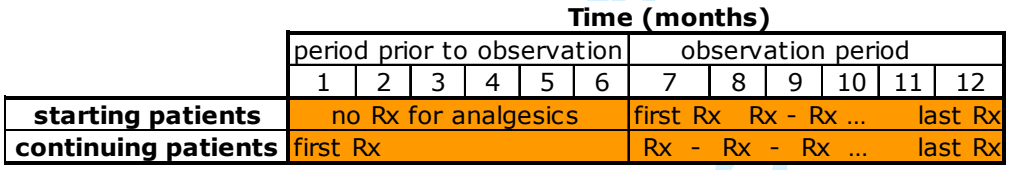
The investigation was carried out by analysing records pertaining to Dutch routine general practice and hospital outpatient treatment settings. Data were obtained from the IMS Health's longitudinal prescription database (Lifelink, affiliate Capelle ad IJssel, The Netherlands)[12]. This data source consists of anonymous longitudinal prescription records from a representative sample of pharmacies and dispensing GPs, covering 73% of the Dutch nationwide medication consumption of outpatients and primary care patients. The computerized medication-dispensing histories contain data regarding dispensed medications, type of prescriber, dispensing date, dispensed amount of medication, prescribed dosage, and length of prescription. Data for each patient were anonymously and independently sampled without linkage of prescriptions to the same patient across pharmacies, because patients in the Netherlands are usually loyal to a single pharmacy[13]. Potential bias caused by patients getting hospitalized, moving to another address or dying was minimized by studying chronic pharmacological pain treatment.

Patient groups

Patient selection started with the identification of chronic users of analgesic medication during a six-month prescription period (hereafter: observation period). Chronic use was

defined as in receipt of analgesic pharmacotherapy during at least two distinct moments covering an interval of at least two months. In order to track medication for other therapeutic indications (i.e. psychotropic medication and pharmaco-treatment for somatic disorders), patients were observed for a period of six months prior to initiation of analgesic treatment. Next, the cohort with chronic use of analgesics was divided into two groups. *Starters* were defined as patients who had not received any analgesics during the six-month period prior to the observation period (hereafter: *Starter group*). Patients who *continued* with pain medication that was already prescribed in the six month before the observation period formed the second group (hereafter: *Continuation group*). The latter group consisted of all patients who had already received analgesics in the first month of the six-month period prior to the observation period, in order to define chronic analgesic treatment before observation (Figure 1).

Figure 1: Starter group and Continuation Group of chronic analgesic treatment



Legend: Schedule of prescriptions (Rx) in Starter group (top) and Continuation group (bottom) of chronic analgesic treatment covering a 12 month period. Months 7 to 12 are the observation period, months 1 to 6 and the pre-observation period.

Data were obtained from the LRx database from month one to twelve as depicted in Figure 1. Statistics were executed at sample level and no projection was applied. Use of other medications (e.g. psychotropic medication and medication for a broad spectrum of somatic conditions) was collected for all patients as well, covering the period of twelve

months, consisting of (i) the pre-observation period (month one to six) and (ii) the observation period (month seven to twelve)).

Escalation of pharmacological pain treatment

All individual prescriptions of analgesics were observed for each patient in both the Starter and Continuation groups during the observation period and during the six months prior to the observation period. At each dispensing date, analgesics were classified *a priori* in five levels, in order of analgesic potency (Figure 2).

Figure 2: Level of analgesic potency*

Level	Medication
Level 1	Paracetamol
Level 2	Prostaglandine inhibitors
Level 3	Anti-epileptics (a,b)
Level 4	Weak opiates (c)
Level 5	Strong opiates (d)

Legend:
* Level 1 (i.e. lowest potency) to level 5 (i.e. highest potency)
(a) Gabapentine, pregabaline and no other anti-epileptic drugs
(b) Carbamazepine, valproic acid, lamotrigine and medication of level 1 or 2
(c) Tramadol, codeine
(d) Methadone, oxycodone, hydromorphone, morphine, buprenorphine, fentanyl, sufentanil, pethidine

Confirmation of escalation during the observation period was based on the comparison of analgesic potency at the first dispensing day and the last day of prescription.

The comparison of first and last prescription of analgesics resulted in the following categories of analgesic escalation: neutral (i.e. no change of analgesic potency), escalation in analgesic treatment (i.e. change to a higher level of analgesic potency), or de-escalation in pharmacological pain treatment (i.e. change to a lower analgesic potency) (Table 1).

If patients received several analgesics on the same day, both the highest and the second highest level of analgesic potency were included in the analyses, in order to define escalation categories (e.g. a change from level 5 plus level 2 to level 5 plus level 3 indicating that escalation had occurred).

Determinants of escalation in analgesic treatment

Three groups of variables hypothesized to act as mediators or confounders were included in the analyses. The first group were patient characteristics such as sex (0=men, 1=women), age (in years) and the location of patient's pharmacy (defined by postal code). The latter variable defined the level of urbanization following the definition of the Dutch Central Bureau of Statistics (level 1 = highest level of urbanisation, to level 5 = rural environment; described in more detail elsewhere[14 15]) and dichotomously defined neighbourhood deprivation (0=no, 1=yes). The dichotomous measure of neighbourhood deprivation was developed by the Netherlands Institute of Research in Healthcare (NIVEL), using socio-economic indicators such as unemployment rate, average income, population density and ethnic variation[16]. Healthcare professionals receive higher levels of funding for their services in these deprived areas[17]. Neighbourhood deprivation was associated with level of urbanization: 86% of the sample living in deprived neighbourhoods lived in an area with the

highest level of urbanization. Moreover, the other patients (14%) living in deprived neighbourhoods lived in an area with the second highest level of urbanization.

Furthermore, psychotropic co-medication was classified into its different classes, and somatic co-medication was similarly grouped in 10 classes (ACE inhibitors, angiotensine II inhibitors; antidiabetics; beta-blockers; calcium antagonists; functional bowel drugs; laxatives; migraine medication; respiratory medication; steroid-antiphlogistics; stomach protectors) (Table 1 to 3). In the Starting group, occurrence of co-medication was time-coded at three levels according to day of first occurrence (i.e. co-medication prescription before start with analgesics, at the same day or after start of analgesic treatment) (Table 2). In the Continuation group, occurrence of co-medication was recorded dichotomously (presence/absence), since it was impossible to distinguish occurrence of co-medication as before or at start of analgesic treatment (Table 3).

Statistical analysis

First, we analysed the pattern of (de-) escalation in analgesic treatment by means of an ordered logistic multivariable regression model with adjusted odds ratios (and 95% confidence interval) using SAS version 9.1[18]. Statistical significance for the model was defined at conventional alpha of 0.05. The dependent variable in this model was the development of a patient's analgesic treatment (de-escalation, neutral, escalation). Independent variables, entered simultaneously in the model, were demographic characteristics, neighbourhood deprivation, and urbanization, use of psychotropic medication and use of somatic medication. In the Starting group, we also included first occurrence of co-medication. The significance of the model and the adjusted R-square value

	Starter group	Continu-ation Group

were used to assess model reliability. Models for Starter and Continuation groups were run separately, given different sample selection criteria. Proportional odds were assumed in the models of escalation and de-escalation of analgesic treatment, and analyses inspected for violation of this assumption. If a determinant was positively associated with escalation of analgesics, absence of this variable was associated negatively with escalation or positively with de-escalation in analgesic treatment (and vice versa). This offered advantage compared to separate models for escalation and de-escalation (such as consistency of model estimates) and avoided double use of patients with a neutral development of analgesic treatment.

Results

Overall, 449,410 patients were included, of which 166,374 were in the Starter group and 283,036 in the Continuation group. The baseline characteristics of both groups are shown in table 1.

Table 1: Baseline characteristics of the patient population with chronic analgesic treatment

		Deprived	Urbanicity[1]	Urbancity	Deprived	Urbanicity	Urbanicity
		nb.hoods	1	2-5	nb. hoods	1	2-5
Patients	(Absolute)	12,485	45,458	120,916	21,799	78,358	204,678
Change in	Analgesics[2]						
	De-escalation	13.3%	12.1%	10.4%	13.2%	12.5%	11.2%
	Neutral	70.1%	71.6%	74.5%	70.0%	71.4%	73.7%
	Escalation	16.5%	16.3%	15.1%	16.8%	16.1%	15.1%
Gender	Male	39.8%	39.3%	40.3%	36.7%	35.2%	34.6%
	Female	60.2%	60.7%	59.7%	63.3%	64.8%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	1.8%	1.6%	1.8%
	26-40	23.8%	19.2%	16.3%	14.0%	10.8%	9.7%
	41-65	50.0%	49.6%	50.9%	56.9%	53.4%	51.8%
	65-85	19.8%	25.2%	26.2%	27.3%	34.2%	36.7%
First	Analgesics						
	Level 1	3.2%	3.9%	4.0%	3.0%	3.8%	4.1%
	Level 2	64.8%	66.6%	72.6%	47.8%	47.1%	53.6%
	Level 3	2.2%	2.5%	2.6%	6.4%	8.1%	8.9%
	Level 4	27.4%	24.2%	18.3%	36.1%	33.9%	27.6%
	Level 5	2.4%	2.9%	2.6%	6.8%	7.2%	5.9%
	level 4/5	29.8%	27.0%	20.8%	42.8%	41.1%	33.5%
Last	Analgesics						
	Level 1	3.4%	3.9%	4.0%	3.4%	4.1%	4.3%
	Level 2	61.9%	63.0%	68.4%	44.5%	44.1%	50.1%
	Level 3	3.0%	3.3%	3.4%	7.0%	8.4%	9.2%
	Level 4	27.6%	24.6%	18.9%	36.8%	34.5%	28.4%
	Level 5	4.1%	5.2%	5.3%	8.3%	9.0%	7.9%
	Level 4/5	31.7%	29.8%	24.2%	45.1%	43.4%	36.3%
Concomitant	Medication[3]						
	Any concomitant drug	78.8%	79.0%	77.3%	89.3%	89.6%	88.0%
	Migraine medication	3.9%	3.6%	3.8%	5.9%	5.2%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	51.6%	53.2%	50.2%
	TCA	5.2%	5.0%	5.0%	9.5%	9.4%	9.6%
	Other AD	2.4%	2.0%	1.6%	4.0%	3.3%	2.7%
	Antipsychotics total	4.1%	3.9%	3.1%	6.7%	6.1%	4.9%
	Antipsychotics atypical	2.4%	2.2%	1.5%	4.1%	3.5%	2.5%
	Antipsychotics classic	2.0%	2.1%	1.8%	3.2%	3.2%	2.7%
	Burpropion	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.4%	0.4%
	Sedatives	27.0%	29.0%	27.4%	41.5%	43.4%	40.6%
	SNRI	2.6%	2.4%	2.2%	4.5%	4.0%	3.5%
	SSRI	7.5%	7.0%	6.4%	10.3%	10.0%	9.0%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.3%	0.5%	0.4%
	Any somatic medication	72.3%	72.6%	71.0%	83.0%	82.9%	81.7%
	Cardiovascular medication[4]	30.9%	31.4%	30.8%	35.2%	34.9%	34.9%
	Other Somatic medication[5]	65.2%	65.5%	64.0%	76.9%	76.7%	75.4%

Legend: Patient characteristics are presented as percentages (e.g. age, gender, level of analgesic treatment, change in analgesic treatment (e.g. escalation, de-escalation, and neutral development of prescriptions), and concomitant medication). Absolute patient numbers are presented for the Starter and the Continuation group of chronic analgesic treatment concerning level of urbanicity and for neighbourhood deprivation.

(1) Urbanicity = Urbanization (level 1 = highest level of urbanization; level 5 = rural environment)

(2) Change in pain medication from first to last prescription (neutral = no change in level of potency, escalation = change to a higher level of analgesic potency, de-escalation = change to lower analgesic potency)

(3) Concomitant drug use, observed during a period of 12 month

(4) Cardiovascular medication: beta-blocker, calcium antagonist, ACE inhibitor, angiotensine II inhibitor

(5) Gastro-intestinal medication: anti-diabetics, steroid-antiphogistics, respiratory medication

About 7.6% of all escalating patients were residing in a deprived neighbourhood, and approximately 27.6% were living in the most densely populated areas (urbanization level 1) (Table 1). The majority was female, and there were more patients showing escalation (15.4%) than de-escalation (11.3%) of analgesic treatment. The majority of patients continued a neutral analgesic treatment regime (73.3%) (Table 1). Most of the patients were treated at level 2 or level 4 of analgesic potency. Almost all patients were using other medications, regardless of the different categories in table 1 (84.5%). Around half were using psychotropic medication (45.2%), most were using somatic co-medication (78.1%), and more than a third were using both (38.8%) (Table 1).

The Starter group mainly initiated an analgesic at level 2 (70.9%) and level 4 (19.9), whereas only 2.6% directly initiated at level 5. However, analgesic potency level 4 and 5 increased up to 20.5% respectively 5.2% by the time of the last prescription in the Starter group (Table 1).

In the Continuation group, patients already received analgesics at a higher level of potency at inclusion compared to the last observed level of medication potency in the Starter group. Level 4 and 5 was observed in 35.6% at the start of the observation period, increasing to 38.3% at the end of observation period (Table 1).

Escalation of analgesic treatment was observed more often in deprived neighbourhoods and the most densely populated areas (16.8% and 16.1% in the

Continuation group, respectively 16.5% and 16.3% in the Starting group) compared to lower densely populated areas (15.1%) and non-deprived neighbourhoods (15.3.%) (Table 1). The proportion of patients with neutral development of analgesic treatment was lower in deprived neighbourhoods and areas with the highest degree of urbanization compared to less densely populated areas (Table 1).

In the Starter group, escalation was positively associated with lower level of first observed pain medication. Escalation was furthermore associated, in a dose-response fashion, with level of urbanization (highest adjusted Odds Ratio (OR) 1.24 at level 1; 95% Confidence Interval (CI) 1.18 to 1.30; compared to reference level 5) (Table 2). Furthermore, a weak but independent association existed between escalation and neighbourhood deprivation (OR 1.06; 95% CI 1.02 to 1.11) (Table 2). Use of tricyclic antidepressants (TCA), mood stabilizers (OR 1.36; 95% CI 1.07 to 1.42), sedatives, cardiovascular medication (OR 1.16; 95% CI 1.13 to 1.19) and medications for other somatic conditions was associated with analgesics escalation, when prescribed *before* start of analgesics (Table 2). Similarly, in the Starter group, escalation of analgesic treatment was also associated with the use of selective noradrenalin serotonin reuptake inhibitors (SNRI), sedatives (OR 1.82; 95% CI 1.74 to 1.89), TCA (OR 2.19; 95% CI 2.03 to 2.36), and antipsychotics (OR 2.43; 95% CI 2.19 to 2.68) when prescribed *after* start of analgesics (Table 2). Negative associations with escalation (i.e. positive association with de-escalation) were apparent for younger age, female sex, and pharmacological migraine treatment. Furthermore, use of antipsychotics was negatively associated with escalation if started *simultaneously* with analgesic treatment (OR 0.70; 95% CI 0.58 to 0.84) (Table 2).

The use of selective serotonin reuptake inhibitors (SSRI), before, at or after start of analgesic treatment was not associated with escalation of analgesics in the Starter group (Table 2).

Table 2: Associations with escalation[1] in pharmacological pain treatment for the *Starter Group* of chronic analgesic treatment

Exposure		Adj. Odds Ratio	Significance[2]	95% CI[3]	
				Lower	Upper
Analgesics	Level 1	58.23	*	53.60	63.27
	Level 2	17.92	*	16.75	19.16
	Level 3	4.66	*	4.23	5.14
	Level 4	1.36	*	1.27	1.45
	Level 5	Reference		-	-
Gender	Female	0.97	*	0.95	0.99
	Male	Reference		0.00	0.00
Age (years)	15-25	0.73	*	0.69	0.77
	26-40	0.81	*	0.78	0.84
	41-65	0.87	*	0.85	0.90
	66-85	Reference		-	-
Urbanization[4]	1	1.24	*	1.18	1.30
	2	1.16	*	1.11	1.22
	3	1.11	*	1.06	1.17
	4	1.07	*	1.02	1.13
	5	Reference		-	-
Deprived	Yes	1.07	*	1.02	1.11
Neighbourhood	No	Reference		-	-
SNRI	[5]Before start of analgesics	1.05	-	0.96	1.14
	Same start date	1.28	-	0.97	1.69
	After analgesics started	1.26	*	1.09	1.45
	None	Reference		-	-
SSRI	Before start of analgesics	0.97	-	0.92	1.02
	Same start date	0.97	-	0.83	1.15
	After analgesics started	1.07	-	0.97	1.18
	None	Reference		-	-
TCA	Before start of analgesics	1.23	*	1.15	1.32
	Same start date	1.32	*	1.12	1.54
	After analgesics started	2.19	*	2.03	2.36
	None	Reference		-	-
Other AD	Before start of analgesics	1.03	-	0.93	1.15
	Same start date	0.93	-	0.71	1.21
	After analgesics started	1.22	*	1.06	1.42
	None	Reference		-	-
Antipsychotics	Before start of analgesics	0.92	-	0.85	1.01
	Same start date	0.69	*	0.58	0.83
	After analgesics started	2.42	*	2.18	2.67
	None	Reference		-	-
Mood stabilizers	Before start of analgesics	1.40	*	1.10	1.79
	Same start date	0.91	-	0.43	1.89
	After analgesics started	0.71	-	0.39	1.31
	None	Reference		-	-
Sedatives	Before start of analgesics	1.24	*	1.20	1.28
	Same start date	1.25	*	1.18	1.33
	After analgesics started	1.82	*	1.74	1.89
	None	Reference		-	-
Cardio-Vascular drugs	Before start of analgesics	1.16	*	1.13	1.19
	Same start date	0.86	*	0.79	0.95
	After analgesics started	1.35	*	1.26	1.45
	None	Reference		-	-
Other Somatic drugs	Before start of analgesics	1.25	*	1.22	1.29
	Same start date	1.11	*	1.07	1.15
	After analgesics started	1.19	*	1.15	1.23
	None	Reference		-	-
Migraine medication	Before start of analgesics	0.83	*	0.77	0.89
	Same start date	0.95	-	0.78	1.17
	After analgesics started	0.91	-	0.81	1.02
	None	Reference		-	-

(1) Escalation = change to a higher level of analgesic potency
(2) Significant variable, p-value<0.05
(3) 95% CI: confidence interval
(4) 1 = highest level of urbanization, 5 = rural environment
(5) Starting date of medication (before, at the same day or after start of analgesics)

In the Continuation group, escalation of analgesics was positively associated with lowest levels of first observed analgesics. Furthermore, escalation was associated with level of urbanization in a dose response fashion (highest adjusted OR 1.19 at level 1; 95% CI 1.14 to 1.23; compared to reference level 5) (Table 3). There was also an association between escalation and deprived neighbourhoods, use of SSRI, SNRI, TCA, all antipsychotics, and sedatives (OR 1.31; 95% CI 1.29 to 1.33) as well as use of somatic co-medication (OR 1.12; 95% CI 1.10 to 1.14) (Table 3). De-escalation was associated with female sex, younger age, treatment of migraine, and use of second-generation antipsychotics (OR 0.80; 95% CI 0.70 to 0.91) (Table 3).

Table 3: Associations with escalation[1] in pharmacological pain treatment for the *Continuation Group* of chronic analgesic treatment

Exposure		Adjusted Odds Ratio	Significance[2]	95% CI[3] Lower	Upper
Analgesics	Level 1	16.00	*	15.20	16.85
	Level 2	7.87	*	7.59	8.16
	Level 3	3.14	*	3.00	3.28
	Level 4	1.55	*	1.50	1.61
	Level 5	Reference		-	-
Gender	Female	0.96	*	0.94	0.98
	Male	Reference		-	-
Age (years)	15-25	0.91	*	0.85	0.97
	26-40	0.98		0.95	1.01
	41-65	0.99		0.97	1.01
	66-85	Reference		-	-
Urbanization[4]	1	1.18	*	1.14	1.23
	2	1.14	*	1.10	1.17
	3	1.08	*	1.04	1.12
	4	1.05	*	1.01	1.09
	5	Reference		-	-
Deprived Neighbourhood	Yes	1.04	*	1.01	1.08
	No	Reference		-	-
SNRI	Total	1.19	*	1.02	1.40
	High dosage	0.95		0.82	1.10
	Low dosage	0.99		0.89	1.11
SSRI	Total	1.03	*	1.004	1.07
TCA	Total	1.19	*	1.06	1.32
	High dosage	1.07		0.97	1.17
	Low dosage	1.12	*	1.01	1.25
Other AD		1.08	*	1.03	1.14
Antipsychotics	Total	1.24	*	1.08	1.43
	Classic	1.01		0.88	1.15
	Atypical	0.80	*	0.70	0.91
Mood stabilizers		0.97		0.85	1.10
Sedatives		1.31	*	1.29	1.34
Migraine		0.95	*	0.91	0.99
Cardio Vascular Drugs		1.12	*	1.10	1.14
Other Somatic Drug classes		1.12	*	1.10	1.14

(1) Escalation = change to a higher level of analgesic potency
(2) Significant variable, p-value<0.05
(3) 95% CI: confidence interval
(4) 1 = highest level of urbanization

Discussion

Escalation of chronic analgesic treatment was observed more often in urban areas and, independently, deprived neighbourhoods within urban areas, suggesting pain outcomes either are associated with individual characteristics that are more prevalent in urban and deprived areas, or subject to contextual influences, like area-level stress or social fragmentation, regardless of individual level characteristics. One individual level variable that may explain part of the association with urbanicity and deprivation is socio-economic status[19 20], which was not available for inclusion in the model. Nevertheless, the fact that the association with urbanicity remained with deprivation adjusted for in the same model, suggests that urban effects may not be reducible entirely to individual-level socio-economic status.

Regardless of the underlying mechanism, results clearly echo findings of unconfounded higher rates of poor mental health in urban and deprived neighbourhood environments[3 4 21], and suggest that the outcome of mental suffering associated with somatic disorders shows similar predictable variation. Functional pain syndromes and psychiatric disorders show high levels of interdependency[22-27], and psychiatric conditions enhance severity of somatic symptoms[28]. Thus, part of the mechanism underlying the association between pharmacological pain escalation and urban environment may be explained by urbanization increasing the risk for mental ill health. This hypothesis is supported by the findings, as in both the Starter and the Continuation groups, escalation of chronic analgesic treatment was associated not only with urban environment and neighbourhood deprivation, but also with prescription of various psychotropic medications prescribed in association. In general, the positive association of escalating analgesic treatment with psychotropic medication was as strong or even stronger than the association

with prescribed somatic co-medication, with the exception of the observed de-escalating effect, in the Continuation group, of second-generation antipsychotics, which possess powerful analgesic properties[29 30]. This is accordance with the literature, given the fact that psychiatric conditions can enhance symptom severity in somatic patients[28], which sometimes may impact even more that the somatic condition itself[31].

However, the question remains to what degree escalation of analgesic treatment and its association with psychotropic medication reflects therapeutic efforts to remedy pain, treatment of psychiatric comorbidity, or a cause of psychopathology. In the Starter and the Continuation group of chronic analgesic treatment, escalation of analgesics was consistently and positively associated with the use of TCA. This prescription habit may reflect routine paradigms in the pharmacological treatment of pain syndromes[10 23 32-34]. However, given the evidence regarding TCA's efficacy in pain conditions, negative rather than positive associations with escalation of analgesics should have been expected. More likely, since the association with TCAs was as strong as the association of sedatives with analgesic escalation, it may be a reflection of affective or addictive comorbidity in persistent pain, for instance in vulnerable cases of opiate-induced sensitization, tolerance and hyperalgesia[35-41]. Moreover, escalation of analgesic treatment in starters of chronic analgesic treatment was even more strongly associated with the use of TCA, sedatives, SNRI and antipsychotics, if prescribed *after* the start of analgesics. One explanation for stronger associations of escalation in analgesics with the use of psychotropic medication if started *after* initiation of analgesic treatment may be that psychotropic medication was prescribed in the event of psychiatric comorbidity occurring later in course of the syndrome occasioning the pain. This may be considered likely, since many patients diagnosed with pain syndromes are suffering from mood or anxiety disorders and functional somatic complaints[37 42]. Furthermore, under-

detection of psychiatric comorbidity may occur early in the course of comorbid psychiatric conditions[25 27 28].

On the other hand, the strong association of psychotropic medication with escalation of analgesics *after* start of analgesic treatment may reflect a direct effect of the psychopharmacological intervention itself. Recent findings suggest that not opiates but serotonin may be involved in the development of persisting pain[43 44]. This may also explain why antidepressants show stronger positive associations with escalation of analgesic treatment if started later, after the initial prescription of analgesics.

According to the literature[23 32-35 45], negative associations of particularly antidepressants with escalation of chronic analgesic treatment might have been expected. As mentioned earlier, under-detection of psychiatric conditions early in the course of analgesic treatment or effects of the pharmacological intervention itself may explain that this is not the case[24 27 37 46]. Nevertheless, there are negative associations with escalation of chronic analgesic treatment in, for example, pharmacological migraine treatment. Moreover, the use of antipsychotics was negatively associated with analgesic escalation for the Starter group if prescribed after start of analgesic treatment. In the Continuation group, de-escalation was specifically associated with the use of atypical antipsychotics. This outcome is interesting and deserves further investigation, given that limited evidence for the efficacy of antipsychotics in pain conditions already exists[29 30].

The results of the current study should be seen in the light of several limitations. The use of routine data rather than a targeted data collection could have caused more random error resulting in type II error. Unidentified confounding may have played a role, as randomization was not possible and pre-post designs are sensitive to effects of unmeasured

changes affecting outcome measures over time. Another limitation is the lack of outcomes other than urbanization, psychotropic medication or somatic co-medication. For instance, there were no estimates regarding care consumption or illness-related sick leave. Changes in patient-related outcomes like illness severity, global functioning, quality of life and treatment satisfaction should also form part of prospective evaluations. Furthermore, this study only collected data over a twelve-month period. Affect and pain monitoring deserves longer evaluation. Finally, due to the study design, associations do not allow for causal inference.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Numerous observational studies have observed higher rates of poor mental health in urban and deprived neighbourhood environments.

Pain syndromes and psychiatric disorders show high levels of interdependency, and psychiatric conditions enhance severity of somatic symptoms.

WHAT THIS STUDY ADDS

Escalation of chronic analgesic treatment in persistent pain is associated with urban environments and deprived neighbourhoods, and occurs in a context of increased levels of psychotropic medications, suggesting persistent pain outcomes are associated with area influences affecting mental health.

Contributors: CL, SB and JvO were principal investigators of the study. SB analysed the data in collaboration with CL, JvO, and JS. CL and JvO drafted the paper. All authors contributed to

subsequent drafts of the paper, including the final version. JvO is guarantor.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, with the exception of above-mentioned funding to IMS Health for data analysis; no financial relationships with any organisation that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

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Level	Medication
Level 1	Paracetamol
Level 2	Prostaglandine inhibitors
Level 3	Anti-epileptics (a,b)
Level 4	Weak opiates (c)
Level 5	Strong opiates (d)

Time (months)

	period prior to observation						observation period					
	1	2	3	4	5	6	7	8	9	10	11	12
starting patients	no Rx for analgesics						first Rx	Rx - Rx ...				last Rx
continuing patients	first Rx						Rx - Rx - Rx ...					last Rx

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found DONE
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported DONE
Objectives	3	State specific objectives, including any prespecified hypotheses DONE
Methods		
Study design	4	Present key elements of study design early in the paper DONE
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection DONE
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up DONE *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable DONE
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group DONE
Bias	9	Describe any efforts to address potential sources of bias DONE
Study size	10	Explain how the study size was arrived at DONE
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why DONE
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding DONE
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed DONE
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram DONE
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders DONE
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) DONE
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time DONE
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included DONE
		(*b*) Report category boundaries when continuous variables were categorized DONE
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives DONE
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias DONE
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence DONE
Generalisability	21	Discuss the generalisability (external validity) of the study results DONE
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based DONE

Original article

Urbanisation and neighbourhood deprivation impact chronic pharmacological pain treatment - a large scale longitudinal cohort study in the Netherlands

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Abstract:

Objective: To examine whether urbanization and neighbourhood deprivation would impact chronic pharmacological pain treatment in terms of greater probability of analgesic escalation, predicted by prescriptions of psychotropic medication.

Design: Longitudinal analysis of a population-based routine prescription database in the Netherlands.

Setting: Representative sample of pharmacies and dispensing general practitioners, covering 73% of the Dutch nationwide medication consumption in primary care and outpatients.

Participants: 449,410 patients aged 15-85 years were included, of whom 166,374 were in the *Starter group* and 283,036 in the *Continuation group* of chronic analgesic treatment.

Main outcome measure: Escalation of analgesics (i.e. change to a higher level of analgesic potency, classified in five levels) in association with urbanization and dichotomous neighbourhood deprivation was analysed over a six-month observation period.

Results: In both *Starter* and *Continuation* groups, escalation was positively associated with urbanization in a dose response fashion (Starter group: OR (urbanization level 1 compared to level 5): 1.24; 95% CI 1.18 to 1.30; Continuation group: OR 1.19; 95% CI 1.14 to 1.23). A weak but independent association was apparent with neighbourhood deprivation (Starter group: OR 1.06; 95% CI 1.02 to 1.11; Continuation group: OR 1.04; 95% CI 1.01 to 1.08). Use of somatic and particularly psychotropic co-medication was independently associated with escalation in both groups.

Conclusion: Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of psychotropic medication prescriptions, suggesting pain outcomes are influenced by area influences affecting mental health.

Introduction

The validity of the well-known epidemiological association between urban environment and mental health[1-3] is supported by work showing that urban living is associated with increased amygdala activity[4], a key region in the regulation of stress, affective experience and pain[5 6]. Pain is the natural comorbid mental experience of somatic conditions[7 8]. In turn, pain is strongly influenced by comorbid mental disorders[9 10]. Given evidence of urban impact on risk for mental disorders, including psychiatric medication prescriptions[11], we hypothesized that pain outcomes, indexed through prescriptions, would be poorer in urban environments and disadvantaged urban neighbourhoods. Pain outcomes were examined at the level of primary care and specialist outpatient care and defined in two ways: (i) escalation of analgesic treatment (i.e. prescription of more potent analgesics) and (ii) co-prescription of psychotropic medication in addition to analgesic treatment.

Objective

We examined the hypothesis that chronic pharmacological pain treatment of outpatients and patients in primary care would show escalation of analgesics in association with the level of urbanization and neighbourhood index of deprivation. It was predicted that the highest levels of urbanization and neighbourhood deprivation would be associated with escalation of analgesic treatment to more potent pain medication (e.g. tramadol, morphine, methadone, etc.), while lower levels of urbanization and neighbourhood deprivation would be associated with less potent analgesics (e.g. paracetamol, aspirin, ibuprofen, etc.). Furthermore, we examined the hypothesis that escalation of analgesics would predict prescriptions of psychotropic medication (e.g. antidepressants, antipsychotics, mood

stabilizers, etc.) in patients prescribed chronic analgesic treatment. Study hypotheses were specified before inspection of the data.

Method

Data collection

The investigation was carried out by analysing records pertaining to Dutch routine general practice and hospital outpatient treatment settings. Data were obtained from the IMS Health's longitudinal prescription database (Lifelink, affiliate Capelle ad IJssel, The Netherlands)[12]. This data source consists of anonymous longitudinal prescription records from a representative sample of pharmacies and dispensing GPs, covering 73% of the Dutch nationwide medication consumption of outpatients and primary care patients. The computerized medication-dispensing histories contain data regarding dispensed medications, type of prescriber, dispensing date, dispensed amount of medication, prescribed dosage, and length of prescription. Data for each patient were anonymously and independently sampled without linkage of prescriptions to the same patient across pharmacies, because patients in the Netherlands are usually loyal to a single pharmacy[13]. Potential bias caused by patients getting hospitalized, moving to another address or dying was minimized by studying chronic pharmacological pain treatment.

Patient groups

Patient selection started with the identification of chronic users of analgesic medication during a six-month prescription period (hereafter: observation period). Chronic use was

defined as in receipt of analgesic pharmacotherapy during at least two distinct moments covering an interval of at least two months. In order to track medication for other therapeutic indications (i.e. psychotropic medication and pharmaco-treatment for somatic disorders), patients were observed for a period of six months prior to initiation of analgesic treatment. Next, the cohort with chronic use of analgesics was divided into two groups. *Starters* were defined as patients who had not received any analgesics during the six-month period prior to the observation period (hereafter: *Starter group*). Patients who *continued* with pain medication that was already prescribed in the six month before the observation period formed the second group (hereafter: *Continuation group*). The latter group consisted of all patients who had already received analgesics in the first month of the six-month period prior to the observation period, in order to define chronic analgesic treatment before observation (Figure 1).

Figure 1: Starter group and Continuation Group of chronic analgesic treatment

Insert Figure 1

Legend: Schedule of prescriptions (Rx) in Starter group (top) and Continuation group (bottom) of chronic analgesic treatment covering a 12 month period. Months 7 to 12 are the observation period, months 1 to 6 and the pre-observation period.

Data were obtained from the LRx database from month one to twelve as depicted in Figure 1. Statistics were executed at sample level and no projection was applied. Use of other medications (e.g. psychotropic medication and medication for a broad spectrum of somatic conditions) was collected for all patients as well, covering the period of twelve

months, consisting of (i) the pre-observation period (month one to six) and (ii) the observation period (month seven to twelve)).

Escalation of pharmacological pain treatment

All individual prescriptions of analgesics were observed for each patient in both the Starter and Continuation groups during the observation period and during the six months prior to the observation period. At each dispensing date, analgesics were classified *a priori* in five levels, in order of analgesic potency (Figure 2).

Figure 2: Level of analgesic potency*

Insert Figure 2

Legend:
* Level 1 (i.e. lowest potency) to level 5 (i.e. highest potency)
(a) Gabapentine, pregabaline and no other anti-epileptic drugs
(b) Carbamazepine, valproic acid, lamotrigine and medication of level 1 or 2
(c) Tramadol, codeine
(d) Methadone, oxycodone, hydromorphone, morphine, buprenorphine, fentanyl, sufentanil, pethidine

Confirmation of escalation during the observation period was based on the comparison of analgesic potency at the first dispensing day and the last day of prescription. The comparison of first and last prescription of analgesics resulted in the following categories of analgesic escalation: neutral (i.e. no change of analgesic potency), escalation in analgesic treatment (i.e. change to a higher level of analgesic potency), or de-escalation in pharmacological pain treatment (i.e. change to a lower analgesic potency) (Table 1).

If patients received several analgesics on the same day, both the highest and the second highest level of analgesic potency were included in the analyses, in order to define escalation categories (e.g. a change from level 5 plus level 2 to level 5 plus level 3 indicating that escalation had occurred).

Determinants of escalation in analgesic treatment

Three groups of variables hypothesized to act as mediators or confounders were included in the analyses. The first group were patient characteristics such as sex (0=men, 1=women), age (in years) and the location of patient's pharmacy (defined by postal code). The latter variable defined the level of urbanization following the definition of the Dutch Central Bureau of Statistics (level 1 = highest level of urbanisation, to level 5 = rural environment; described in more detail elsewhere[14 15]) and dichotomously defined neighbourhood deprivation (0=no, 1=yes). The dichotomous measure of neighbourhood deprivation was developed by the Netherlands Institute of Research in Healthcare (NIVEL), using socio-economic indicators such as unemployment rate, average income, population density and ethnic variation[16]. Healthcare professionals receive higher levels of funding for their services in these deprived areas[17]. Neighbourhood deprivation was associated with level of urbanization: 86% of the sample living in deprived neighbourhoods lived in an area with the highest level of urbanization. Moreover, the other patients (14%) living in deprived neighbourhoods lived in an area with the second highest level of urbanization.

Furthermore, psychotropic co-medication was classified into its different classes, and somatic co-medication was similarly grouped in 10 classes (ACE inhibitors, angiotensine II inhibitors; antidiabetics; beta-blockers; calcium antagonists; functional bowel drugs;

laxatives; migraine medication; respiratory medication; steroid-antiphlogistics; stomach protectors) (Table 1 to 3). In the Starting group, occurrence of co-medication was time-coded at three levels according to day of first occurrence (i.e. co-medication prescription before start with analgesics, at the same day or after start of analgesic treatment) (Table 2). In the Continuation group, occurrence of co-medication was recorded dichotomously (presence/absence), since it was impossible to distinguish occurrence of co-medication as before or at start of analgesic treatment (Table 3).

Statistical analysis

First, we analysed the pattern of (de-) escalation in analgesic treatment by means of an ordered logistic multivariable regression model with adjusted odds ratios (and 95% confidence interval) using SAS version 9.1[18]. Statistical significance for the model was defined at conventional alpha of 0.05. The dependent variable in this model was the development of a patient's analgesic treatment (de-escalation, neutral, escalation). Independent variables, entered simultaneously in the model, were demographic characteristics, neighbourhood deprivation, and urbanization, use of psychotropic medication and use of somatic medication. In the Starting group, we also included first occurrence of co-medication. The significance of the model and the adjusted R-square value were used to assess model reliability. Models for Starter and Continuation groups were run separately, given different sample selection criteria. Proportional odds were assumed in the models of escalation and de-escalation of analgesic treatment, and analyses inspected for violation of this assumption. If a determinant was positively associated with escalation of analgesics, absence of this variable was associated negatively with escalation or positively

	Starter group	Continu-ation Group

with de-escalation in analgesic treatment (and vice versa). This offered advantage compared to separate models for escalation and de-escalation (such as consistency of model estimates) and avoided double use of patients with a neutral development of analgesic treatment.

Results

Overall, 449,410 patients were included, of which 166,374 were in the Starter group and 283,036 in the Continuation group. The baseline characteristics of both groups are shown in table 1.

Table 1: Baseline characteristics of the patient population with chronic analgesic treatment

		Deprived	Urbanicity[1]	Urbancity	Deprived	Urbanicity	Urbanicity
		nb.hoods	1	2-5	nb. hoods	1	2-5
Patients	(Absolute)	12,485	45,458	120,916	21,799	78,358	204,678
Change in	Analgesics[2]						
	De-escalation	13.3%	12.1%	10.4%	13.2%	12.5%	11.2%
	Neutral	70.1%	71.6%	74.5%	70.0%	71.4%	73.7%
	Escalation	16.5%	16.3%	15.1%	16.8%	16.1%	15.1%
Gender	Male	39.8%	39.3%	40.3%	36.7%	35.2%	34.6%
	Female	60.2%	60.7%	59.7%	63.3%	64.8%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	1.8%	1.6%	1.8%
	26-40	23.8%	19.2%	16.3%	14.0%	10.8%	9.7%
	41-65	50.0%	49.6%	50.9%	56.9%	53.4%	51.8%
	65-85	19.8%	25.2%	26.2%	27.3%	34.2%	36.7%
First	Analgesics						
	Level 1	3.2%	3.9%	4.0%	3.0%	3.8%	4.1%
	Level 2	64.8%	66.6%	72.6%	47.8%	47.1%	53.6%
	Level 3	2.2%	2.5%	2.6%	6.4%	8.1%	8.9%
	Level 4	27.4%	24.2%	18.3%	36.1%	33.9%	27.6%
	Level 5	2.4%	2.9%	2.6%	6.8%	7.2%	5.9%
	level 4/5	29.8%	27.0%	20.8%	42.8%	41.1%	33.5%
Last	Analgesics						
	Level 1	3.4%	3.9%	4.0%	3.4%	4.1%	4.3%
	Level 2	61.9%	63.0%	68.4%	44.5%	44.1%	50.1%
	Level 3	3.0%	3.3%	3.4%	7.0%	8.4%	9.2%
	Level 4	27.6%	24.6%	18.9%	36.8%	34.5%	28.4%
	Level 5	4.1%	5.2%	5.3%	8.3%	9.0%	7.9%
	Level 4/5	31.7%	29.8%	24.2%	45.1%	43.4%	36.3%
Concomitant	Medication[3]						
	Any concomitant drug	78.8%	79.0%	77.3%	89.3%	89.6%	88.0%
	Migraine medication	3.9%	3.6%	3.8%	5.9%	5.2%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	51.6%	53.2%	50.2%
	TCA	5.2%	5.0%	5.0%	9.5%	9.4%	9.6%
	Other AD	2.4%	2.0%	1.6%	4.0%	3.3%	2.7%
	Antipsychotics total	4.1%	3.9%	3.1%	6.7%	6.1%	4.9%
	Antipsychotics atypical	2.4%	2.2%	1.5%	4.1%	3.5%	2.5%
	Antipsychotics classic	2.0%	2.1%	1.8%	3.2%	3.2%	2.7%
	Burpropion	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.4%	0.4%
	Sedatives	27.0%	29.0%	27.4%	41.5%	43.4%	40.6%
	SNRI	2.6%	2.4%	2.2%	4.5%	4.0%	3.5%
	SSRI	7.5%	7.0%	6.4%	10.3%	10.0%	9.0%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.3%	0.5%	0.4%
	Any somatic medication	72.3%	72.6%	71.0%	83.0%	82.9%	81.7%
	Cardiovascular medication[4]	30.9%	31.4%	30.8%	35.2%	34.9%	34.9%
	Other Somatic medication[5]	65.2%	65.5%	64.0%	76.9%	76.7%	75.4%

Legend: Patient characteristics are presented as percentages (e.g. age, gender, level of analgesic treatment, change in analgesic treatment (e.g. escalation, de-escalation, and neutral development of prescriptions), and concomitant medication). Absolute patient numbers are presented for the Starter and the Continuation group of chronic analgesic treatment concerning level of urbanicity and for neighbourhood deprivation.

(1) Urbanicity = Urbanization (level 1 = highest level of urbanization; level 5 = rural environment)

(2) Change in pain medication from first to last prescription (neutral = no change in level of potency, escalation = change to a higher level of analgesic potency, de-escalation = change to lower analgesic potency)

(3) Concomitant drug use, observed during a period of 12 month

(4) Cardiovascular medication: beta-blocker, calcium antagonist, ACE inhibitor, angiotensine II inhibitor

(5) Gastro-intestinal medication: anti-diabetics, steroid-antiphogistics, respiratory medication

About 7.6% of all escalating patients were residing in a deprived neighbourhood, and approximately 27.6% were living in the most densely populated areas (urbanization level 1) (Table 1). The majority was female, and there were more patients showing escalation (15.4%) than de-escalation (11.3%) of analgesic treatment. The majority of patients continued a neutral analgesic treatment regime (73.3%) (Table 1). Most of the patients were treated at level 2 or level 4 of analgesic potency. Almost all patients were using other medications, regardless of the different categories in table 1 (84.5%). Around half were using psychotropic medication (45.2%), most were using somatic co-medication (78.1%), and more than a third were using both (38.8%) (Table 1).

The Starter group mainly initiated an analgesic at level 2 (70.9%) and level 4 (19.9), whereas only 2.6% directly initiated at level 5. However, analgesic potency level 4 and 5 increased up to 20.5% respectively 5.2% by the time of the last prescription in the Starter group (Table 1).

In the Continuation group, patients already received analgesics at a higher level of potency at inclusion compared to the last observed level of medication potency in the Starter group. Level 4 and 5 was observed in 35.6% at the start of the observation period, increasing to 38.3% at the end of observation period (Table 1).

Escalation of analgesic treatment was observed more often in deprived neighbourhoods and the most densely populated areas (16.8% and 16.1% in the

Continuation group, respectively 16.5% and 16.3% in the Starting group) compared to lower densely populated areas (15.1%) and non-deprived neighbourhoods (15.3.%) (Table 1). The proportion of patients with neutral development of analgesic treatment was lower in deprived neighbourhoods and areas with the highest degree of urbanization compared to less densely populated areas (Table 1).

In the Starter group, escalation was positively associated with lower level of first observed pain medication. Escalation was furthermore associated, in a dose-response fashion, with level of urbanization (highest adjusted Odds Ratio (OR) 1.24 at level 1; 95% Confidence Interval (CI) 1.18 to 1.30; compared to reference level 5) (Table 2). Furthermore, a weak but independent association existed between escalation and neighbourhood deprivation (OR 1.06; 95% CI 1.02 to 1.11) (Table 2). Use of tricyclic antidepressants (TCA), mood stabilizers (OR 1.36; 95% CI 1.07 to 1.42), sedatives, cardiovascular medication (OR 1.16; 95% CI 1.13 to 1.19) and medications for other somatic conditions was associated with analgesics escalation, when prescribed *before* start of analgesics (Table 2). Similarly, in the Starter group, escalation of analgesic treatment was also associated with the use of selective noradrenalin serotonin reuptake inhibitors (SNRI), sedatives (OR 1.82; 95% CI 1.74 to 1.89), TCA (OR 2.19; 95% CI 2.03 to 2.36), and antipsychotics (OR 2.43; 95% CI 2.19 to 2.68) when prescribed *after* start of analgesics (Table 2). Negative associations with escalation (i.e. positive association with de-escalation) were apparent for younger age, female sex, and pharmacological migraine treatment. Furthermore, use of antipsychotics was negatively associated with escalation if started *simultaneously* with analgesic treatment (OR 0.70; 95% CI 0.58 to 0.84) (Table 2).

The use of selective serotonin reuptake inhibitors (SSRI), before, at or after start of analgesic treatment was not associated with escalation of analgesics in the Starter group (Table 2).

Table 2: Associations with escalation[1] in pharmacological pain treatment for the *Starter Group* of chronic analgesic treatment

Exposure		Adj. Odds Ratio	Significance[2]	95% CI[3]	
				Lower	Upper
Analgesics	Level 1	58.23	*	53.60	63.27
	Level 2	17.92	*	16.75	19.16
	Level 3	4.66	*	4.23	5.14
	Level 4	1.36	*	1.27	1.45
	Level 5	Reference		-	-
Gender	Female	0.97	*	0.95	0.99
	Male	Reference		0.00	0.00
Age (years)	15-25	0.73	*	0.69	0.77
	26-40	0.81	*	0.78	0.84
	41-65	0.87	*	0.85	0.90
	66-85	Reference		-	-
Urbanization[4]	1	1.24	*	1.18	1.30
	2	1.16	*	1.11	1.22
	3	1.11	*	1.06	1.17
	4	1.07	*	1.02	1.13
	5	Reference		-	-
Deprived	Yes	1.07	*	1.02	1.11
Neighbourhood	No	Reference		-	-
SNRI	[5]Before start of analgesics	1.05	-	0.96	1.14
	Same start date	1.28	-	0.97	1.69
	After analgesics started	1.26	*	1.09	1.45
	None	Reference		-	-
SSRI	Before start of analgesics	0.97	-	0.92	1.02
	Same start date	0.97	-	0.83	1.15
	After analgesics started	1.07	-	0.97	1.18
	None	Reference		-	-
TCA	Before start of analgesics	1.23	*	1.15	1.32
	Same start date	1.32	*	1.12	1.54
	After analgesics started	2.19	*	2.03	2.36
	None	Reference		-	-
Other AD	Before start of analgesics	1.03	-	0.93	1.15
	Same start date	0.93	-	0.71	1.21
	After analgesics started	1.22	*	1.06	1.42
	None	Reference		-	-
Antipsychotics	Before start of analgesics	0.92	-	0.85	1.01
	Same start date	0.69	*	0.58	0.83
	After analgesics started	2.42	*	2.18	2.67
	None	Reference		-	-
Mood stabilizers	Before start of analgesics	1.40	*	1.10	1.79
	Same start date	0.91	-	0.43	1.89
	After analgesics started	0.71	-	0.39	1.31
	None	Reference		-	-
Sedatives	Before start of analgesics	1.24	*	1.20	1.28
	Same start date	1.25	*	1.18	1.33
	After analgesics started	1.82	*	1.74	1.89
	None	Reference		-	-
Cardio-Vascular drugs	Before start of analgesics	1.16	*	1.13	1.19
	Same start date	0.86	*	0.79	0.95
	After analgesics started	1.35	*	1.26	1.45
	None	Reference		-	-
Other Somatic drugs	Before start of analgesics	1.25	*	1.22	1.29
	Same start date	1.11	*	1.07	1.15
	After analgesics started	1.19	*	1.15	1.23
	None	Reference		-	-
Migraine medication	Before start of analgesics	0.83	*	0.77	0.89
	Same start date	0.95	-	0.78	1.17
	After analgesics started	0.91	-	0.81	1.02
	None	Reference		-	-

(1) Escalation = change to a higher level of analgesic potency
(2) Significant variable, p-value<0.05
(3) 95% CI: confidence interval
(4) 1 = highest level of urbanization, 5 = rural environment
(5) Starting date of medication (before, at the same day or after start of analgesics)

In the Continuation group, escalation of analgesics was positively associated with lowest levels of first observed analgesics. Furthermore, escalation was associated with level of urbanization in a dose response fashion (highest adjusted OR 1.19 at level 1; 95% CI 1.14 to 1.23; compared to reference level 5) (Table 3). There was also an association between escalation and deprived neighbourhoods, use of SSRI, SNRI, TCA, all antipsychotics, and sedatives (OR 1.31; 95% CI 1.29 to 1.33) as well as use of somatic co-medication (OR 1.12; 95% CI 1.10 to 1.14) (Table 3). De-escalation was associated with female sex, younger age, treatment of migraine, and use of second-generation antipsychotics (OR 0.80; 95% CI 0.70 to 0.91) (Table 3).

Table 3: Associations with escalation[1] in pharmacological pain treatment for the *Continuation Group* of chronic analgesic treatment

Exposure		Adjusted Odds	Significance[2]	95%	CI[3]
		Ratio		Lower	Upper
Analgesics	Level 1	16.00	*	15.20	16.85
	Level 2	7.87	*	7.59	8.16
	Level 3	3.14	*	3.00	3.28
	Level 4	1.55	*	1.50	1.61
	Level 5	Reference		-	-
Gender	Female	0.96	*	0.94	0.98
	Male	Reference		-	-
Age (years)	15-25	0.91	*	0.85	0.97
	26-40	0.98		0.95	1.01
	41-65	0.99		0.97	1.01
	66-85	Reference		-	-
Urbanization[4]	1	1.18	*	1.14	1.23
	2	1.14	*	1.10	1.17
	3	1.08	*	1.04	1.12
	4	1.05	*	1.01	1.09
	5	Reference		-	-
Deprived Neighbourhood	Yes	1.04	*	1.01	1.08
	No	Reference		-	-
SNRI	Total	1.19	*	1.02	1.40
	High dosage	0.95		0.82	1.10
	Low dosage	0.99		0.89	1.11
SSRI	Total	1.03	*	1.004	1.07
TCA	Total	1.19	*	1.06	1.32
	High dosage	1.07		0.97	1.17
	Low dosage	1.12	*	1.01	1.25
Other AD		1.08	*	1.03	1.14
Antipsychotics	Total	1.24	*	1.08	1.43
	Classic	1.01		0.88	1.15
	Atypical	0.80	*	0.70	0.91
Mood stabilizers		0.97		0.85	1.10
Sedatives		1.31	*	1.29	1.34
Migraine		0.95	*	0.91	0.99
Cardio Vascular Drugs		1.12	*	1.10	1.14
Other Somatic Drug classes		1.12	*	1.10	1.14

(1) Escalation = change to a higher level of analgesic potency
(2) Significant variable, p-value<0.05
(3) 95% CI: confidence interval
(4) 1 = highest level of urbanization

Discussion

Escalation of chronic analgesic treatment was observed more often in urban areas and, independently, deprived neighbourhoods within urban areas, suggesting pain outcomes either are associated with individual characteristics that are more prevalent in urban and deprived areas, or subject to contextual influences, like area-level stress or social fragmentation, regardless of individual level characteristics. One individual level variable that may explain part of the association with urbanicity and deprivation is socio-economic status[19 20], which was not available for inclusion in the model. Nevertheless, the fact that the association with urbanicity remained with deprivation adjusted for in the same model, suggests that urban effects may not be reducible entirely to individual-level socio-economic status.

Regardless of the underlying mechanism, results clearly echo findings of unconfounded higher rates of poor mental health in urban and deprived neighbourhood environments[3 4 21], and suggest that the outcome of mental suffering associated with somatic disorders shows similar predictable variation. Functional pain syndromes and psychiatric disorders show high levels of interdependency[22-27], and psychiatric conditions enhance severity of somatic symptoms[28]. Thus, part of the mechanism underlying the association between pharmacological pain escalation and urban environment may be explained by urbanization increasing the risk for mental ill health. This hypothesis is supported by the findings, as in both the Starter and the Continuation groups, escalation of chronic analgesic treatment was associated not only with urban environment and neighbourhood deprivation, but also with prescription of various psychotropic medications prescribed in association. In general, the positive association of escalating analgesic treatment with psychotropic medication was as strong or even stronger than the association

with prescribed somatic co-medication, with the exception of the observed de-escalating effect, in the Continuation group, of second-generation antipsychotics, which possess powerful analgesic properties[29 30]. This is accordance with the literature, given the fact that psychiatric conditions can enhance symptom severity in somatic patients[28], which sometimes may impact even more that the somatic condition itself[31].

However, the question remains to what degree escalation of analgesic treatment and its association with psychotropic medication reflects therapeutic efforts to remedy pain, treatment of psychiatric comorbidity, or a cause of psychopathology. In the Starter and the Continuation group of chronic analgesic treatment, escalation of analgesics was consistently and positively associated with the use of TCA. This prescription habit may reflect routine paradigms in the pharmacological treatment of pain syndromes[10 23 32-34]. However, given the evidence regarding TCA's efficacy in pain conditions, negative rather than positive associations with escalation of analgesics should have been expected. More likely, since the association with TCAs was as strong as the association of sedatives with analgesic escalation, it may be a reflection of affective or addictive comorbidity in persistent pain, for instance in vulnerable cases of opiate-induced sensitization, tolerance and hyperalgesia[35-41]. Moreover, escalation of analgesic treatment in starters of chronic analgesic treatment was even more strongly associated with the use of TCA, sedatives, SNRI and antipsychotics, if prescribed *after* the start of analgesics. One explanation for stronger associations of escalation in analgesics with the use of psychotropic medication if started *after* initiation of analgesic treatment may be that psychotropic medication was prescribed in the event of psychiatric comorbidity occurring later in course of the syndrome occasioning the pain. This may be considered likely, since many patients diagnosed with pain syndromes are suffering from mood or anxiety disorders and functional somatic complaints[37 42]. Furthermore, under-

detection of psychiatric comorbidity may occur early in the course of comorbid psychiatric conditions[25 27 28].

On the other hand, the strong association of psychotropic medication with escalation of analgesics *after* start of analgesic treatment may reflect a direct effect of the psychopharmacological intervention itself. Recent findings suggest that not opiates but serotonin may be involved in the development of persisting pain[43 44]. This may also explain why antidepressants show stronger positive associations with escalation of analgesic treatment if started later, after the initial prescription of analgesics.

According to the literature[23 32-35 45], negative associations of particularly antidepressants with escalation of chronic analgesic treatment might have been expected. As mentioned earlier, under-detection of psychiatric conditions early in the course of analgesic treatment or effects of the pharmacological intervention itself may explain that this is not the case[24 27 37 46]. Nevertheless, there are negative associations with escalation of chronic analgesic treatment in, for example, pharmacological migraine treatment. Moreover, the use of antipsychotics was negatively associated with analgesic escalation for the Starter group if prescribed after start of analgesic treatment. In the Continuation group, de-escalation was specifically associated with the use of atypical antipsychotics. This outcome is interesting and deserves further investigation, given that limited evidence for the efficacy of antipsychotics in pain conditions already exists[29 30].

The results of the current study should be seen in the light of several limitations. The use of routine data rather than a targeted data collection could have caused more random error resulting in type II error. Unidentified confounding may have played a role, as randomization was not possible and pre-post designs are sensitive to effects of unmeasured

changes affecting outcome measures over time. Another limitation is the lack of outcomes other than urbanization, psychotropic medication or somatic co-medication. For instance, there were no estimates regarding care consumption or illness-related sick leave. Changes in patient-related outcomes like illness severity, global functioning, quality of life and treatment satisfaction should also form part of prospective evaluations. Furthermore, this study only collected data over a twelve-month period. Affect and pain monitoring deserves longer evaluation. Finally, due to the study design, associations do not allow for causal inference.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Numerous observational studies have observed higher rates of poor mental health in urban and deprived neighbourhood environments.

Pain syndromes and psychiatric disorders show high levels of interdependency, and psychiatric conditions enhance severity of somatic symptoms.

WHAT THIS STUDY ADDS

Escalation of chronic analgesic treatment in persistent pain is associated with urban environments and deprived neighbourhoods, and occurs in a context of increased levels of psychotropic medications, suggesting persistent pain outcomes are associated with area influences affecting mental health.

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subsequent drafts of the paper, including the final version. JvO is guarantor.

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	Starter	Continu-

Table 1: Baseline characteristics of the patient population with chronic analgesic treatment

		group			ation group		
		Deprived nb.hoods	Urbanicity[1] 1	Urbancity 2-5	Deprived nb. hoods	Urbanicity 1	Urbanic 2-5
Patients	(Absolute)	12,485	45,458	120,916	21,799	78,358	204,67
Change in	Analgesics[2]						
	De-escalation	13.3%	12.1%	10.4%	13.2%	12.5%	11.2%
	Neutral	70.1%	71.6%	74.5%	70.0%	71.4%	73.7%
	Escalation	16.5%	16.3%	15.1%	16.8%	16.1%	15.1%
Gender	Male	39.8%	39.3%	40.3%	36.7%	35.2%	34.6%
	Female	60.2%	60.7%	59.7%	63.3%	64.8%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	1.8%	1.6%	1.8%
	26-40	23.8%	19.2%	16.3%	14.0%	10.8%	9.7%
	41-65	50.0%	49.6%	50.9%	56.9%	53.4%	51.8%
	65-85	19.8%	25.2%	26.2%	27.3%	34.2%	36.7%
First	Analgesics						
	Level 1	3.2%	3.9%	4.0%	3.0%	3.8%	4.1%
	Level 2	64.8%	66.6%	72.6%	47.8%	47.1%	53.6%
	Level 3	2.2%	2.5%	2.6%	6.4%	8.1%	8.9%
	Level 4	27.4%	24.2%	18.3%	36.1%	33.9%	27.6%
	Level 5	2.4%	2.9%	2.6%	6.8%	7.2%	5.9%
	level 4/5	29.8%	27.0%	20.8%	42.8%	41.1%	33.5%
Last	Analgesics						
	Level 1	3.4%	3.9%	4.0%	3.4%	4.1%	4.3%
	Level 2	61.9%	63.0%	68.4%	44.5%	44.1%	50.1%
	Level 3	3.0%	3.3%	3.4%	7.0%	8.4%	9.2%
	Level 4	27.6%	24.6%	18.9%	36.8%	34.5%	28.4%
	Level 5	4.1%	5.2%	5.3%	8.3%	9.0%	7.9%
	Level 4/5	31.7%	29.8%	24.2%	45.1%	43.4%	36.3%
Concomitant	Medication[3]						
	Any concomitant drug	78.8%	79.0%	77.3%	89.3%	89.6%	88.0%
	Migraine medication	3.9%	3.6%	3.8%	5.9%	5.2%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	51.6%	53.2%	50.2%
	TCA	5.2%	5.0%	5.0%	9.5%	9.4%	9.6%
	Other AD	2.4%	2.0%	1.6%	4.0%	3.3%	2.7%
	Antipsychotics total	4.1%	3.9%	3.1%	6.7%	6.1%	4.9%
	Antipsychotics atypical	2.4%	2.2%	1.5%	4.1%	3.5%	2.5%
	Antipsychotics classic	2.0%	2.1%	1.8%	3.2%	3.2%	2.7%
	Burpropion	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.4%	0.4%
	Sedatives	27.0%	29.0%	27.4%	41.5%	43.4%	40.6%
	SNRI	2.6%	2.4%	2.2%	4.5%	4.0%	3.5%
	SSRI	7.5%	7.0%	6.4%	10.3%	10.0%	9.0%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.3%	0.5%	0.4%
	Any somatic medication	72.3%	72.6%	71.0%	83.0%	82.9%	81.7%
	Cardiovascular medication[4]	30.9%	31.4%	30.8%	35.2%	34.9%	34.9%
	Other Somatic medication[5]	65.2%	65.5%	64.0%	76.9%	76.7%	75.4%

Legend: Patient characteristics are presented as percentages (e.g. age, gender, level of analgesic treatment, change in analgesic treatment (e.g. escalation, de-escalation, and neutral development of prescriptions), and concomitant medication). Absolute patient numbers are presented for the Starter and the Continuation group of chronic analgesic treatment concerning level of urbanicity and for neighbourhood deprivation.

(1) Urbanicity = Urbanization (level 1 = highest level of urbanization; level 5 = rural environment)

(2) Change in pain medication from first to last prescription (neutral = no change in level of potency, escalation = change to a higher level of analgesic potency, de-escalation = change to lower analgesic potency)

(3) Concomitant drug use, observed during a period of 12 month

(4) Cardiovascular medication: beta-blocker, calcium antagonist, ACE inhibitor, angiotensine II inhibitor

(5) Gastro-intestinal medication: anti-diabetics, steroid-antiphogistics, respiratory medication

Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in pharmacological pain treatment - a longitudinal population-based study in the Netherlands

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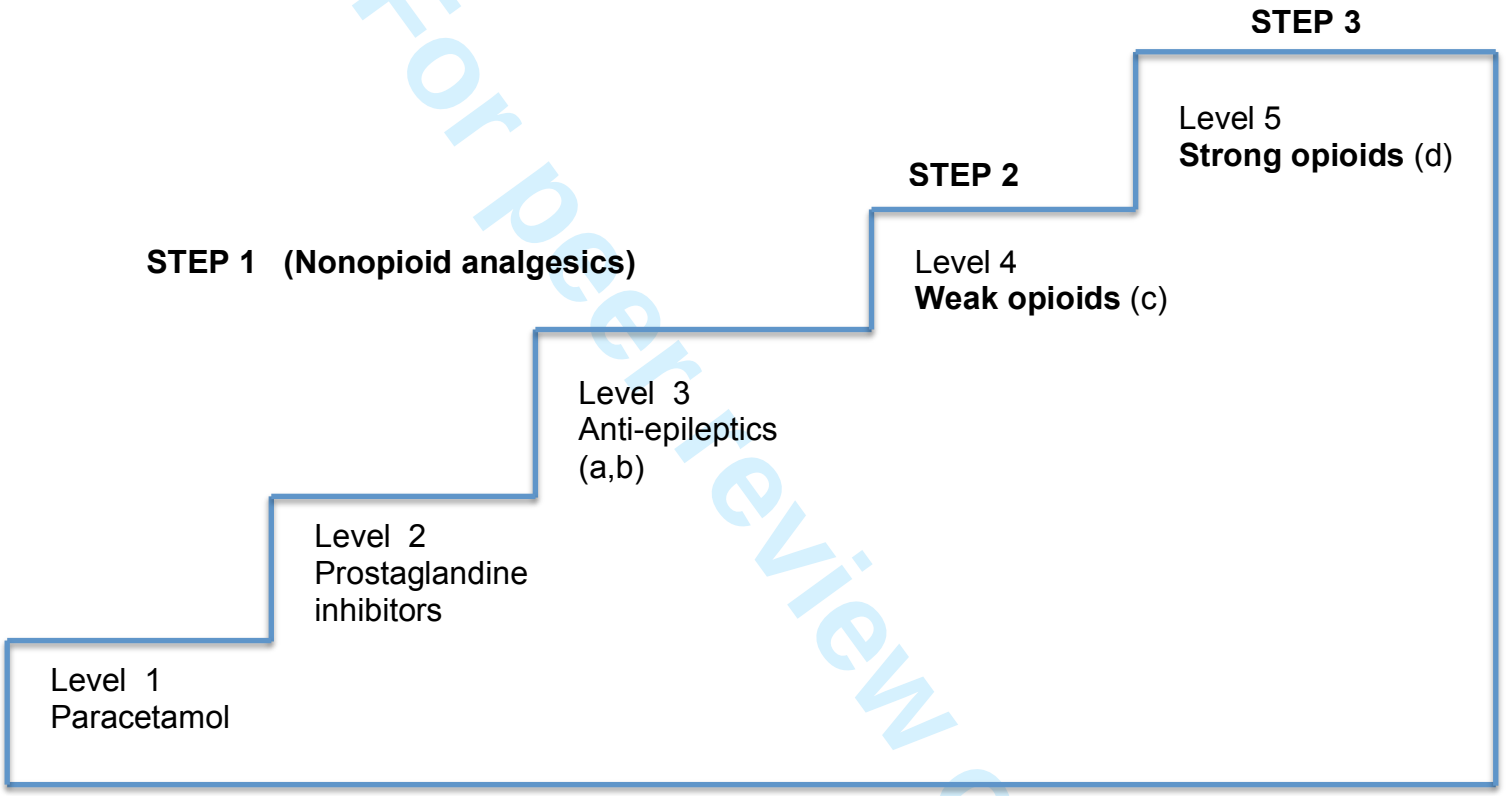
	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found DONE
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported DONE
Objectives	3	State specific objectives, including any prespecified hypotheses DONE
Methods		
Study design	4	Present key elements of study design early in the paper DONE
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection DONE
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up DONE *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable DONE
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group DONE
Bias	9	Describe any efforts to address potential sources of bias DONE
Study size	10	Explain how the study size was arrived at DONE
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why DONE
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding DONE
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed DONE
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram DONE
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders DONE
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) DONE
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time DONE
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included DONE
		(*b*) Report category boundaries when continuous variables were categorized DONE
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives DONE
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias DONE
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence DONE
Generalisability	21	Discuss the generalisability (external validity) of the study results DONE
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based DONE

	Time (months)											
	period prior to observation						observation period					
	1	2	3	4	5	6	7	8	9	10	11	12
starting patients	no Rx for analgesics						first Rx	Rx - Rx ...				last Rx
continuing patients	first Rx						Rx - Rx - Rx ...					last Rx



Original article

Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in pharmacological pain treatment - a longitudinal population-based study in the Netherlands

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Abstract:

Objective: To examine whether urbanisation and neighbourhood deprivation are associated with analgesic escalation in chronic pharmacological pain treatment, and whether escalation is associated with prescription of psychotropic medications.

Design: Longitudinal analysis of a population-based routine dispensing database in the Netherlands.

Setting: Representative sample of pharmacies, covering 73% of the Dutch nationwide medication consumption in the primary care and hospital outpatient settings.

Participants: 449,410 patients aged 15-85 years were included, of whom 166,374 were in the *Starter group* and 283,036 in the *Continuation group* of chronic analgesic treatment.

Main outcome measure: Escalation of analgesics (i.e. change to a higher level of analgesic potency, classified in five levels) in association with urbanisation (five levels) and dichotomous neighbourhood deprivation, analysed over a six-month observation period.

Methods: Ordered logistic multivariate model evaluating analgesic treatment.

Results: In both *Starter* and *Continuation* groups, escalation was positively associated with urbanisation in a dose-response fashion (Starter group: OR (urbanisation level 1 compared to level 5): 1.24; 95% CI 1.18 to 1.30; Continuation group: OR 1.19; 95% CI 1.14 to 1.23). A weak association was apparent with neighbourhood deprivation (Starter group: OR 1.06; 95% CI 1.02 to 1.11; Continuation group: OR 1.04; 95% CI 1.01 to 1.08). Use of somatic and particularly psychotropic co-medication was associated with escalation in both groups.

Conclusion: Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medications, suggesting pain outcomes in part reflect area influences affecting mental health.

Introduction

The validity of the well-known epidemiological association between urban environment and mental health[1-3] is supported by work showing that urban living is associated with increased amygdala activity[4], a key region in the regulation of stress, affective experience and pain[5 6]. Pain is the natural comorbid mental experience of somatic conditions[7 8]. In turn, pain is strongly influenced by comorbid common mental disorders particulary affective disorders[9 10]. Given evidence of urban impact on risk for common mental disorders[11], including psychiatric medication prescriptions[12], we hypothesized that pain outcomes, indexed through prescriptions, would be poorer in urban environments and disadvantaged urban neighbourhoods. Pain outcomes were examined at the level of primary care and specialist outpatient care and defined in two ways: (i) escalation of analgesic treatment (i.e. prescription of more potent analgesics) and (ii) co-prescription of psychotropic medication in addition to analgesic treatment.

Objective

We examined the hypothesis that chronic pharmacological pain treatment of hospital outpatients and patients in primary care would show escalation of analgesics in association with the level of urbanisation and neighbourhood index of deprivation. It was predicted that the highest levels of urbanisation and neighbourhood deprivation would be associated with escalation of analgesic treatment to more potent pain medication (e.g. tramadol, morphine, methadone, etc.). Furthermore, we examined the hypothesis that prescriptions of psychotropic medication (e.g. antidepressants, antipsychotics, mood stabilizers, etc.) would

be associated with escalation or de-escalation of analgesics in patients prescribed chronic analgesic treatment. Study hypotheses were specified before inspection of the data.

Method

Data collection

The investigation was carried out by analysing records pertaining to Dutch routine general practice and hospital outpatient treatment settings. Data were obtained from the IMS Health's longitudinal prescription database (Lifelink, affiliate Capelle ad IJssel, The Netherlands)[13]. This data source consists of anonymous longitudinal prescription records from a representative sample of pharmacies and dispensing GPs, covering 73% of the Dutch nationwide medication consumption of outpatients and primary care patients. The computerized *medication-dispensing histories* contain data regarding dispensed medications, type of prescriber, dispensing date, dispensed amount of medication, prescribed dosage, and length of prescription. Data for each patient were anonymously and independently sampled without linkage of prescriptions to the same patient across pharmacies, because patients in the Netherlands are usually loyal to a single pharmacy[14]. Furthermore, research from the Dutch Foundation for Pharmaceutical Statistics (SFK) revealed that in the Netherlands, almost all patients make use of a pharmacy located in their area of living. Eighty-two percent of patients are living in a radius of 3 kilometres from their pharmacy[15]. Potential bias caused by patients getting hospitalized, moving to another address or dying was minimized by studying chronic pharmacological pain treatment, because there were dispensing records for these patients during the whole study period.

Patient groups

Patient selection started with the identification of chronic users of analgesic medication during a six-month prescription period (hereafter: observation period). Chronic use was defined as in receipt of analgesic pharmacotherapy during at least two distinct moments covering an interval of at least two months. In order to track medication for other therapeutic indications (i.e. psychotropic medication and pharmaco-treatment for somatic disorders), patients were observed for a period of six months prior to initiation of analgesic treatment. Next, the cohort with chronic use of analgesics was divided into two groups. *Starters* were defined as patients who had not received any analgesics during the six-month period prior to the observation period (hereafter: *Starter group*). Patients who *continued* with pain medication that was already prescribed in the six month before the observation period formed the second group (hereafter: *Continuation group*). The latter group consisted of all patients who had already received analgesics in the first month of the six-month period prior to the observation period, in order to define chronic analgesic treatment before observation. All data captured a calendar period from May 2008 to September 2009 (Figure 1).

Figure 1: Starter group and Continuation Group of chronic analgesic treatment

Insert Figure 1

Legend: Schedule of prescriptions (Rx) in Starter group (top) and Continuation group (bottom) of chronic analgesic treatment covering a 12 month period. Months 7 to 12 are the observation period; months 1 to 6 are the pre-observation period.

Data were obtained from the LRx database from month one to twelve as depicted in Figure 1.. Use of other medications (e.g. psychotropic medication and medication for a broad spectrum of somatic conditions) was collected for all patients as well, covering the period of twelve months, consisting of (i) the pre-observation period (month one to six) and (ii) the observation period (month seven to twelve)).

Escalation of pharmacological pain treatment

All individual prescriptions of analgesics were observed for each patient in both the Starter and Continuation groups during the observation period and during the six months prior to the observation period. At each dispensing date, analgesics were classified *a priori* in five levels, in order of analgesic potency (Figure 2). Five escalation levels were provided, based on a minor adaptation of the 3-step WHO-analgesic ladder[16]. Levels 5 and 4 are identical to WHO steps 3 (strong opioids) and 2 (weak opioids), respectively. WHO step 1 (non-opioid analgesics) was refined, in order to enable further and clinically relevant differentiation between non-opioid analgesics (level 1: paracetamol, level 2: prostaglandin inhibitors, level 3: anticonvulsants) [16-20]. Furthermore, anti-epileptics were divided in anticonvulsants predominantly prescribed in pain conditions (level 3a: gabapentin and pregabalin) and anticonvulsants with best evidence for epilepsy treatment (level 3b: carbamazepine, valproic acid, lamotrigine)[19-21]. In order to avoid prescription for indications of mood stabilisation or epilepsy, the latter group was classified at level 3b only if prescribed in combination with analgesic medication at level 1 or 2 (i.e. pain indication) (Figure 2).

Figure 2: 5 levels of analgesic potency, modified from the WHO-analgesic ladder[16]

Insert Figure 2

Legend:
Level 1 (i.e. lowest potency) to level 5 (i.e. highest potency)
(a) Gabapentine, pregabaline in the absence of other anti-epileptic drugs
(b) Carbamazepine, valproic acid, lamotrigine in combination with medication at level 1 or 2
(c) Tramadol, codeine
(d) Methadone, oxycodone, hydromorphone, morphine, buprenorphine, fentanyl, sufentanil, pethidine

Confirmation of escalation was based on the comparison of analgesic potency at the first dispensing day and the last dispensing day within the observation period.

The comparison of first and last prescription of analgesics resulted in the following categories of analgesic escalation: neutral (i.e. no change of analgesic potency), escalation in analgesic treatment (i.e. change to a higher level of analgesic potency), or de-escalation in pharmacological pain treatment (i.e. change to a lower analgesic potency) (Table 1).

If patients received several analgesics on the same day, both the highest and the second highest level of analgesic potency were included in the analyses, in order to define escalation categories (e.g. a change from level 5 plus level 2 to level 5 plus level 3 indicating that escalation had occurred).

Determinants of escalation in analgesic treatment

Three groups of variables hypothesized to act as mediators or confounders were included in the analyses. The first group were patient characteristics such as sex (0=men, 1=women), age (in years) and the location of patient's pharmacy (defined by postal code). The latter variable defined the level of urbanisation following the definition of the Dutch Central

Bureau of Statistics (CBS). Urbanisation is defined by CBS as the number of addresses relative to area surface, conform previous work with this variable in epidemiological studies [22]. Level 1 (i.e. highest level of urbanisation) consists of more than 2500 addresses per square-kilometre (km^2); [level 2 = 1500 to 2500 addresses/km^2, level 3 = 1000 to 1500 addresses/km^2, level 4 = 500 to 1000 addresses/km^2]. Level 5 (i.e. rural environment) consists of less than 500 addresses/km^2; described in more detail elsewhere[23].

Neighbourhood deprivation was defined dichotomously (0=no, 1=yes). The dichotomous measure of neighbourhood deprivation was developed by the Netherlands Institute of Research in Healthcare (NIVEL), using socio-economic indicators such as unemployment rate, average income, population density and ethnic variation. On the basis of empirical research in the Netherlands, NIVEL 's neighbourhood deprivation index (NDI) is calculated as follows: NDI = ((ln percentage unemployed people – 3.0236)/0.37706) – ((ln average income – 2.8641)/0.14441) + ((ln population density – 7.0132)/1.06699) + ((ln percentage people of "non-western" ethnicity)/1.11147). NDIs were expressed continuously by NIVEL from low to high. Furthermore, NIVEL defined a dichotomous measure of deprivation at a cut-off of 5.5% (i.e. 885.000 people), in order to assess trends in the proportion of the Dutch population inhabiting an area with the highest NDI and for use in epidemiological research[24].

Healthcare professionals receive higher levels of funding for their services in these deprived areas[25]. Neighbourhood deprivation was associated with level of urbanization: 86% of the sample living in deprived neighbourhoods lived in an area with the highest level of urbanisation. Moreover, the other patients (14%) living in deprived neighbourhoods lived in an area with the second highest level of urbanisation. The majority (76%) of those living in an area of the highest level of urbanisation did not live in a deprived neighbourhood (Table 1).

Table 1: Sample, stratified by Urbanisation and Neighbourhood Deprivation

		Deprived Neighbourhood		% within	% within
type of patient	Urbanisation	No	Yes	Deprived Nbh	Urbanisation
Starter group	1	34662	10796	86,5%	23,7%
	2	48673	1689	13,5%	3,4%
	3	31107		-	-
	4	28283		-	-
	5	11164		-	-
	total	153889	12485	100,0%	7,5%
Continuation group	1	59714	18644	85,5%	23,8%
	2	81406	3155	14,5%	3,7%
	3	50852		-	-
	4	48511		-	-
	5	20754		-	-
	total	261237	21799	100,0%	7,7%

Legend: The sample is described in absolute numbers for the Starter and the Continuation group, stratified by living in an urbanised area (level 1 to 5), and a dichotomous measure of neighbourhood deprivation. Furthermore, in the last two columns, tabulations are presented for living in a deprived neighbourhood as a function of level of urbanization (e.g. 86.5% of the sample living in deprived neighbourhoods lived in an area with urbanisation level 1/Starter group) and for level of urbanisation as a function of living in a deprived neighbourhood (e.g. a minority (23.8%) of those living in an area pertaining to urbanisation level 1 lived in a deprived neighbourhood/Continuation group).

Furthermore, psychotropic co-medication was classified into its different classes, and somatic co-medication was similarly grouped in 10 classes (ACE inhibitors, angiotensine II inhibitors; antidiabetics; beta-blockers; calcium antagonists; functional bowel drugs; laxatives; migraine medication; respiratory medication; steroid-antiphlogistics; stomach protectors) (Table 1 to 3). In the Starting group, occurrence of co-medication was time-coded at three levels according to the day of first occurrence (i.e. co-medication prescription before start with analgesics, at the same day or after start of analgesic treatment) (Table 2). In the Continuation group, occurrence of co-medication was recorded dichotomously (presence/absence), since it was impossible to distinguish occurrence of co-medication as before or at start of analgesic treatment (Table 3).

Statistical analysis

First, we analysed the pattern of (de-) escalation in analgesic treatment by means of an

ordered logistic multivariable regression model with adjusted odds ratios (and 95% confidence interval) using SAS version 9 [26]. Statistical significance for the model was defined at conventional alpha of 0.05. The dependent variable in this model was the development of a patient's analgesic treatment (de-escalation, neutral, escalation). Independent variables, entered simultaneously in the model, were demographic characteristics, neighbourhood deprivation, and urbanisation, use of psychotropic medication and use of somatic medication. In the Starting group, we also included first occurrence of co-medication. The modeling strategy was to build, first, a fully saturated model (including all variables), in order to avoid missing relevant information by leaving out non-significant variables. Second, backward elimination was carried out to find the best model fit.

Models for Starter and Continuation groups were run separately, given different sample selection criteria. The ordered logistic multivariable regression model was chosen above the multinomial model, as the latter does not consider the natural order in our data regarding development of chronic pain treatment, ranging from de-escalation to neutral to escalation. Proportional odds were assumed in the models of escalation and de-escalation of analgesic treatment, and analyses inspected for violation of this assumption. Test on the proportional odds assumption showed significance, which gave us the confidence to use the ordered logistic model. If a determinant was positively associated with escalation of analgesics, absence of this variable was associated negatively with escalation or positively with de-escalation in analgesic treatment (and vice versa). This offered advantage compared to separate models for escalation and de-escalation (such as consistency of model estimates) and avoided double use of patients with a neutral development of analgesic treatment.

Results

Overall, 449,410 patients were included, of which 166,374 were in the Starter group and 283,036 in the Continuation group. The baseline characteristics of both groups are shown in table 2.

Table 2: Baseline characteristics of the patient population with chronic analgesic treatment

		Starter group			Conti-nuation Group		
		Deprived nb.hoods	Urbanicity[1] 1	Urbancity 2-5	Deprived nb. hoods	Urbanicity 1	Urbanicity 2-5
Patients	(Absolute)	12,485	45,458	120,916	21,799	78,358	204,678
Change in	Analgesics[2]						
	De-escalation	13.3%	12.1%	10.4%	13.2%	12.5%	11.2%
	Neutral	70.1%	71.6%	74.5%	70.0%	71.4%	73.7%
	Escalation	16.5%	16.3%	15.1%	16.8%	16.1%	15.1%
Gender	Male	39.8%	39.3%	40.3%	36.7%	35.2%	34.6%
	Female	60.2%	60.7%	59.7%	63.3%	64.8%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	1.8%	1.6%	1.8%
	26-40	23.8%	19.2%	16.3%	14.0%	10.8%	9.7%
	41-65	50.0%	49.6%	50.9%	56.9%	53.4%	51.8%
	65-85	19.8%	25.2%	26.2%	27.3%	34.2%	36.7%
First	Analgesics						
	Level 1	3.2%	3.9%	4.0%	3.0%	3.8%	4.1%
	Level 2	64.8%	66.6%	72.6%	47.8%	47.1%	53.6%
	Level 3	2.2%	2.5%	2.6%	6.4%	8.1%	8.9%
	Level 4	27.4%	24.2%	18.3%	36.1%	33.9%	27.6%
	Level 5	2.4%	2.9%	2.6%	6.8%	7.2%	5.9%
	level 4/5	29.8%	27.0%	20.8%	42.8%	41.1%	33.5%
Last	Analgesics						
	Level 1	3.4%	3.9%	4.0%	3.4%	4.1%	4.3%
	Level 2	61.9%	63.0%	68.4%	44.5%	44.1%	50.1%
	Level 3	3.0%	3.3%	3.4%	7.0%	8.4%	9.2%
	Level 4	27.6%	24.6%	18.9%	36.8%	34.5%	28.4%
	Level 5	4.1%	5.2%	5.3%	8.3%	9.0%	7.9%
	Level 4/5	31.7%	29.8%	24.2%	45.1%	43.4%	36.3%
Concomitant	Medication[3]						
	Any concomitant drug	78.8%	79.0%	77.3%	89.3%	89.6%	88.0%
	Migraine medication	3.9%	3.6%	3.8%	5.9%	5.2%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	51.6%	53.2%	50.2%
	TCA	5.2%	5.0%	5.0%	9.5%	9.4%	9.6%
	Other AD	2.4%	2.0%	1.6%	4.0%	3.3%	2.7%
	Antipsychotics total	4.1%	3.9%	3.1%	6.7%	6.1%	4.9%
	Antipsychotics atypical	2.4%	2.2%	1.5%	4.1%	3.5%	2.5%
	Antipsychotics classic	2.0%	2.1%	1.8%	3.2%	3.2%	2.7%
	Burpropion	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.4%	0.4%
	Sedatives	27.0%	29.0%	27.4%	41.5%	43.4%	40.6%
	SNRI	2.6%	2.4%	2.2%	4.5%	4.0%	3.5%
	SSRI	7.5%	7.0%	6.4%	10.3%	10.0%	9.0%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.3%	0.5%	0.4%
	Any somatic medication	72.3%	72.6%	71.0%	83.0%	82.9%	81.7%
	Cardiovascular medication[4]	30.9%	31.4%	30.8%	35.2%	34.9%	34.9%
	Other Somatic medication[5]	65.2%	65.5%	64.0%	76.9%	76.7%	75.4%

Legend: Patient characteristics are presented as percentages (e.g. age, gender, level of analgesic treatment, change in analgesic treatment (e.g. escalation, de-escalation, and neutral development of prescriptions), and concomitant medication). Absolute patient numbers are presented for the Starter and the Continuation group of chronic analgesic treatment concerning level of urbanicity and for neighbourhood deprivation.

(1) Urbanicity = Urbanisation (level 1 = highest level of urbanisation; level 5 = rural environment)

(2) Change in pain medication from first to last prescription (neutral = no change in level of potency, escalation = change to a higher level of analgesic potency, de-escalation = change to lower analgesic potency)

(3) Concomitant drug use, observed during a period of 12 month

(4) Cardiovascular medication: beta-blocker, calcium antagonist, ACE inhibitor, angiotensine II inhibitor

(5) Gastro-intestinal medication: anti-diabetics, steroid-antiphogistics, respiratory medication

About 7.6% of all escalating patients were residing in a deprived neighbourhood, and approximately 27.6% were living in an area of the highest level of urbanisation (level 1) (Table 2). The majority were female, and there were more patients showing escalation (15.4%) than de-escalation (11.3%) of analgesic treatment. The majority of patients continued a neutral analgesic treatment regime (73.3%) (Table 2). Most of the patients were treated at level 2 or level 4 of analgesic potency. Almost all patients were using other medications, regardless of the different categories in table 1 (84.5%). Around half were using psychotropic medication (45.2%), most were using somatic co-medication (78.1%), and more than a third were using both (38.8%) (Table 2).

The Starter group mainly initiated an analgesic at level 2 (70.9%) and level 4 (19.9), whereas only 2.6% directly initiated at level 5. However, analgesic potency level 4 and 5 increased up to 20.5% respectively 5.2% by the time of the last prescription in the Starter group (Table 2).

In the Continuation group, patients already received analgesics at a higher level of potency at inclusion compared to the last observed level of medication potency in the Starter group. Level 4 and 5 was observed in 35.6% at the start of the observation period, increasing to 38.3% at the end of observation period (Table 2).

Escalation of analgesic treatment was observed more often in deprived neighbourhoods and in areas of the highest levels of urbanisation (16.8% and 16.1% in the Continuation group, respectively 16.5% and 16.3% in the Starting group) compared to rural areas (15.1%) and non-deprived neighbourhoods (15.3.%) (Table 2). The proportion of patients with neutral development of analgesic treatment was lower in deprived neighbourhoods and areas with the highest degree of urbanisation compared to less densely populated areas (Table 2).

In the Starter group, escalation was positively associated with lower level of first observed pain medication (highest adjusted Odds Ratio (OR) 58.23 at analgesic level 1; 95% Confidence Interval (CI) 53.60 to 63.27; lowest OR 1.36 at analgesic level 4; 95% CI 1.27 to 1.45; compared to reference level 5) (Table 3). Escalation was furthermore associated, in a dose-response fashion, with level of urbanisation (highest adjusted OR 1.24 at urbanisation level 1; 95% CI 1.18 to 1.30; compared to reference level 5) (Table 3). Furthermore, a weak but independent association existed between escalation and neighbourhood deprivation (OR 1.06; 95% CI 1.02 to 1.11) (Table 3). Use of tricyclic antidepressants (TCA), mood stabilizers (OR 1.36; 95% CI 1.07 to 1.42), sedatives, cardiovascular medication (OR 1.16; 95% CI 1.13 to 1.19) and medications for other somatic conditions was associated with analgesics escalation, when prescribed *before* start of analgesics (Table 3). Similarly, in the Starter group, escalation of analgesic treatment was also associated with the use of selective

noradrenalin serotonin reuptake inhibitors (SNRI), sedatives (OR 1.82; 95% CI 1.74 to 1.89), TCA (OR 2.19; 95% CI 2.03 to 2.36), and antipsychotics (OR 2.43; 95% CI 2.19 to 2.68) when prescribed *after* start of analgesics (Table 3). Negative associations with escalation (i.e. positive association with de-escalation) were apparent for younger age, female sex, and pharmacological migraine treatment. Furthermore, use of antipsychotics was negatively associated with escalation if started *simultaneously* with analgesic treatment (OR 0.70; 95% CI 0.58 to 0.84) (Table 3).

The use of selective serotonin reuptake inhibitors (SSRI), before, at or after start of analgesic treatment was not associated with escalation of analgesics in the Starter group (Table 3).

In the Starter group, the original fully saturated model and the model after backward elimination revealed the same variables associated significantly with escalation in chronic pharmacological pain treatment (Table 3).

Table 3: Associations with escalation in pharmacological pain treatment for the *Starter Group* of chronic analgesic treatment

Exposure		Adj. Odds Ratio	95%	CI[1]
			Lower	Upper
Analgesics[2]	Level 1	58.23	53.60	63.27
	Level 2	17.92	16.75	19.16
	Level 3	4.66	4.23	5.14
	Level 4	1.36	1.27	1.45
	Level 5	Reference	-	-
Gender	Female	0.97	0.95	0.99
	Male	Reference	0.00	0.00
Age (years)	15-25	0.73	0.69	0.77
	26-40	0.81	0.78	0.84
	41-65	0.87	0.85	0.90
	66-85	Reference	-	-
Urbanization[3]	1	1.24	1.18	1.30
	2	1.16	1.11	1.22
	3	1.11	1.06	1.17
	4	1.07	1.02	1.13
	5	Reference	-	-
Deprived	Yes	1.07	1.02	1.11
Neighbourhood	No	Reference	-	-
SNRI	[4]Before start of analgesics	1.05	0.96	1.14
	Same start date	1.28	0.97	1.69
	After analgesics started	1.26	1.09	1.45
	None	Reference	-	-
SSRI	Before start of analgesics	0.97	0.92	1.02
	Same start date	0.97	0.83	1.15
	After analgesics started	1.07	0.97	1.18
	None	Reference	-	-
TCA	Before start of analgesics	1.23	1.15	1.32
	Same start date	1.32	1.12	1.54
	After analgesics started	2.19	2.03	2.36
	None	Reference	-	-
Other AD	Before start of analgesics	1.03	0.93	1.15
	Same start date	0.93	0.71	1.21
	After analgesics started	1.22	1.06	1.42
	None	Reference	-	-
Antipsychotics	Before start of analgesics	0.92	0.85	1.01
	Same start date	0.69	0.58	0.83
	After analgesics started	2.42	2.18	2.67
	None	Reference	-	-
Mood stabilizers	Before start of analgesics	1.40	1.10	1.79
	Same start date	0.91	0.43	1.89
	After analgesics started	0.71	0.39	1.31
	None	Reference	-	-
Sedatives	Before start of analgesics	1.24	1.20	1.28
	Same start date	1.25	1.18	1.33
	After analgesics started	1.82	1.74	1.89
	None	Reference	-	-
Cardio-Vascular drugs	Before start of analgesics	1.16	1.13	1.19
	Same start date	0.86	0.79	0.95
	After analgesics started	1.35	1.26	1.45
	None	Reference	-	-
Other Somatic drugs	Before start of analgesics	1.25	1.22	1.29
	Same start date	1.11	1.07	1.15
	After analgesics started	1.19	1.15	1.23
	None	Reference	-	-
Migraine medication	Before start of analgesics	0.83	0.77	0.89
	Same start date	0.95	0.78	1.17
	After analgesics started	0.91	0.81	1.02
	None	Reference	-	-

Legend:

(1) 95% CI: confidence interval
(2) Escalation = change to a higher level of analgesic potency, level 5 = highest level
(3) 1 = highest level of urbanisation, 5 = rural environment
(4) Starting date of medication (before, at the same day or after start of analgesics)

In the Continuation group, escalation of analgesics was positively associated with lowest levels of first observed analgesics (highest adjusted OR 16.00 at analgesic level 1; 95% CI 15.20 to 16.85; lowest OR 1.55 at analgesic level 4; 95% CI 1.50 to 1.61; compared to reference level 5) (Table 4). Furthermore, escalation was associated with level of urbanisation in a dose response fashion (highest adjusted OR 1.19 at level 1; 95% CI 1.14 to 1.23; compared to reference level 5) (Table 4). There was also an association between escalation and deprived neighbourhoods, use of SSRI, SNRI, TCA, all antipsychotics, and sedatives (OR 1.31; 95% CI 1.29 to 1.33) as well as use of somatic co-medication (OR 1.12; 95% CI 1.10 to 1.14) (Table 4). De-escalation was associated with female sex, younger age, treatment of migraine, and use of second-generation antipsychotics (OR 0.80; 95% CI 0.70 to 0.91) (Table 4).

The saturated model showed that 22 out of 29 variables had significant associations. All these variables remained significant in the backward elimination approach. One additional variable displayed a significant association after backward elimination: 'TCA high dosage'. The OR's did not (16 variables), or only minimally (6 variables) differ between the fully saturated model and the backward elimination model. The only variable showing a degree of difference was 'TCA total' (fully saturated model: OR = 1.19 (CI: 1.06 – 1.32); backward elimination model: OR = 1.33 (CI: 1.29 – 1.36)) (Table 4).

Table 4: Associations with escalation in pharmacological pain treatment for the *Continuation Group* of chronic analgesic treatment

Exposure		Adjusted Odds Ratio	95% CI[1] Lower	Upper
Analgesics[2]	Level 1	16.00	15.20	16.85
	Level 2	7.87	7.59	8.16
	Level 3	3.14	3.00	3.28
	Level 4	1.55	1.50	1.61
	Level 5	Reference	-	-
Gender	Female	0.96	0.94	0.98
	Male	Reference	-	-
Age (years)	15-25	0.91	0.85	0.97
	26-40	0.98	0.95	1.01
	41-65	0.99	0.97	1.01
	66-85	Reference	-	-
Urbanization[3]	1	1.18	1.14	1.23
	2	1.14	1.10	1.17
	3	1.08	1.04	1.12
	4	1.05	1.01	1.09
	5	Reference	-	-
Deprived Neighbourhood	Yes	1.04	1.01	1.08
	No	Reference	-	-
SNRI		1.19	1.02	1.40
SSRI		1.03	1.004	1.07
TCA[4]		1.19	1.06	1.32
Other AD		1.08	1.03	1.14
Antipsychotics	Total	1.24	1.08	1.43
	1st generation	1.01	0.88	1.15
	2nd generation	0.80	0.70	0.91
Mood stabilizers		0.97	0.85	1.10
Sedatives		1.31	1.29	1.34
Migraine		0.95	0.91	0.99
Cardio Vascular Drugs		1.12	1.10	1.14
Other Somatic Drug classes		1.12	1.10	1.14

Legend:
(1) 95% CI: confidence interval
(2) Escalation = change to a higher level of analgesic potency, level 5 = highest level
(3) 1 = highest level of urbanisation, 5 = rural environment
(4) TCA total (fully saturated model: OR = 1.19 (CI: 1.06 – 1.32); BWE model: OR = 1.33 (CI: 1.29 – 1.36))

Over time, the escalation process continues even after the first 6 months of chronic analgesic treatment. In the Starter group, opioid-analgesics (level 4/5) were dispensed in 29.8% of patients living in a deprived neighbourhood. In contrast, 42.8% of patients in deprived neighbourhoods used opioids in the Continuation group, after one year of prescription. A similar, but attenuated development was seen at urbanisation level 1 and level 2 to 5 (Table 2).

Discussion

Escalation of chronic analgesic treatment was observed more often in urban areas and deprived neighbourhoods within urban areas, suggesting pain outcomes either are associated with individual characteristics that are more prevalent in urban and deprived areas, or subject to contextual influences, like area-level stress or social fragmentation, regardless of individual level characteristics. One individual level variable that may explain part of the association with urbanicity and deprivation is socio-economic status[27 28], which was not available for inclusion in the model. Nevertheless, the fact that the association with urbanicity remained with deprivation adjusted for in the same model, suggests that urban effects may not be reducible entirely to individual-level socio-economic status. However, the findings could also be attributed to reverse causation, i.e. patients with worsening pain may move into more urban and deprived neighbourhoods as a consequence of being disabled due to ill health. Although unlikely to entirely explain the current findings, it cannot be excluded.

Regardless of the underlying mechanism, results clearly echo findings of unconfounded higher rates of poor mental health in areas of higher levels of urbanisation and greater neighbourhood deprivation[11 29], and suggest that the outcome of mental disorder comorbidity associated with somatic disorders shows similar predictable variation. Functional pain syndromes and psychiatric disorders show high levels of interdependency[30-35], and psychiatric conditions enhance severity of somatic symptoms[36]. Thus, part of the mechanism underlying the association between pharmacological pain escalation and urban environment may be explained by urbanisation increasing the risk for mental ill health. This hypothesis is supported by the findings, as in both the Starter and the Continuation groups, escalation of chronic analgesic treatment was associated not only with urban environment

and neighbourhood deprivation, but also with prescription of various psychotropic medications prescribed in association. In general, the positive association of escalating analgesic treatment with psychotropic medication was as strong or even stronger than the association with prescribed somatic co-medication, with the exception of the observed de-escalating effect, in the Continuation group, of second-generation antipsychotics, which possess powerful analgesic properties[37 38]. This is accordance with the literature, given the fact that psychiatric conditions can enhance symptom severity in somatic patients[36], which sometimes may impact even more that the somatic condition itself[39].

Although the absolute difference between analgesic escalation in the urban vs. less urban environment was small, this difference may be relevant from a public health perspective, given the high rate of painful conditions in the general population. Furthermore, prevention of persistent pain states is relevant with regard to costs[40]. A more effective treatment of persistent pain, including treatment of psychiatric comorbidity, may have a cost-saving effect. Targeting populations with painful conditions for early recognition and treatment of mental health problems may not only be cost-effective from a public health perspective, but also represent an area of considerable unmet clinical need, since opioid escalation is a frequent inflationary development in the treatment of painful conditions[41 42]. Moreover, broadening the pain agenda to a better understanding of associated mental health problems could minimize failed surgery outcomes, for example in patients with undetected mental disorders. For instance, new surgical procedures were found to be more common in chronic back pain (CBP) patients *with* Post-traumatic Stress Disorder compared to CBP patients without[43]. Similarly, depression was demonstrated in 47.4 % of patients with low back pain who had no surgery, in 50% of those with one surgical procedure, and in 62.5 % of those who had undergone surgery more than once[44]. Influencing

central pain sensitization by providing adequate antidepressant treatment in depressive conditions may help prevent surgical escalation.

Odds ratios for escalation of analgesics in relation to original level of analgesics may represent ceiling effects in both starter and continuation groups - patients already at level 5 have nowhere stronger to go; treatment of patients at level 1 at baseline can escalate to stronger medication. Ceiling effects may reflect the pattern of prescribing analgesics in general practice. Given these, it has been suggested that the WHO analgesic ladder is in need of updating[45]. For example, Vargas-Schaffer is broadening the ladder with a 4th surgical step; in the current article, however, we guide attention to treatment aspects related to underestimated mental disorder comorbidity in persistent pain states.

The –speculative- question remains to what degree escalation of analgesic treatment and its association with psychotropic medication reflects therapeutic paradigms to remedy pain, treatment of psychiatric comorbidity, or a cause of psychopathology. In the Starter and the Continuation group of chronic analgesic treatment, escalation of analgesics was consistently and positively associated with the use of TCA. This prescription habit may reflect routine off-label paradigms in the pharmacological treatment of pain syndromes[10 46-48]. However, given the evidence regarding TCA's efficacy in pain conditions, negative rather than positive associations with escalation of analgesics should have been expected. More likely, since the association with TCAs was as strong as the association of sedatives with analgesic escalation, it may be a reflection of affective or addictive comorbidity in persistent pain, for instance in vulnerable cases of opiate-induced sensitization, tolerance and hyperalgesia[49-55]. Our data indicate that escalation may represent an ongoing process after even months of treatment, which occurs not exclusively in the context of environmental

deprivation. Escalation may also be driven to a degree by patient factors such as opioid tolerance, opioid-induced hyperalgesia[52], or disease progression.

Given the literature on this topic[46-50 56], negative associations of particularly antidepressants with escalation of chronic analgesic treatment would have been expected. Nevertheless, negative associations between escalation of chronic analgesic treatment were also found, for example with migraine treatment (Tables 3 and 4). Moreover, the use of antipsychotics was negatively associated with analgesic escalation in the Starter group - if prescribed after start of analgesic treatment. In the Continuation group, de-escalation was specifically associated with the use of second-generation antipsychotics. This outcome is interesting and deserves further investigation, given that limited evidence for the efficacy of antipsychotics in pain conditions already exists[37 38].

The results of the current study should be seen in the light of several limitations. The use of routine data rather than a targeted data collection could have caused more random error resulting in type II error. Unidentified confounding may have played a role, as randomization was not possible and pre-post designs are sensitive to effects of unmeasured changes affecting outcome measures over time. Another limitation is the lack of outcomes other than urbanization, psychotropic medication or somatic co-medication. For instance, there were no estimates regarding care consumption or illness-related sick leave. Changes in patient-related outcomes like illness severity, global functioning, quality of life and treatment satisfaction should also form part of prospective evaluations. The type of data used is subject to the possibility of ecological fallacy: people whose pharmacy is in a deprived or urban neighbourhood do not necessarily experience that level of deprivation or urbanicity. Furthermore, this study only collected data over a twelve-month period. Affect

and pain monitoring deserves longer evaluation. Finally, due to the study design, associations do not allow for causal inference.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Numerous observational studies have observed higher rates of poor mental health in urban and deprived neighbourhood environments.

Pain syndromes and mental disorders show high levels of interdependency, and mental disorders are known to enhance severity of somatic symptoms.

WHAT THIS STUDY ADDS

Escalation of chronic analgesic treatment in persistent pain states is associated with urban environments and deprived neighbourhoods, and occurs in a context of increased levels of psychotropic medication prescribing, suggesting persistent pain outcomes are associated with area influences affecting mental health.

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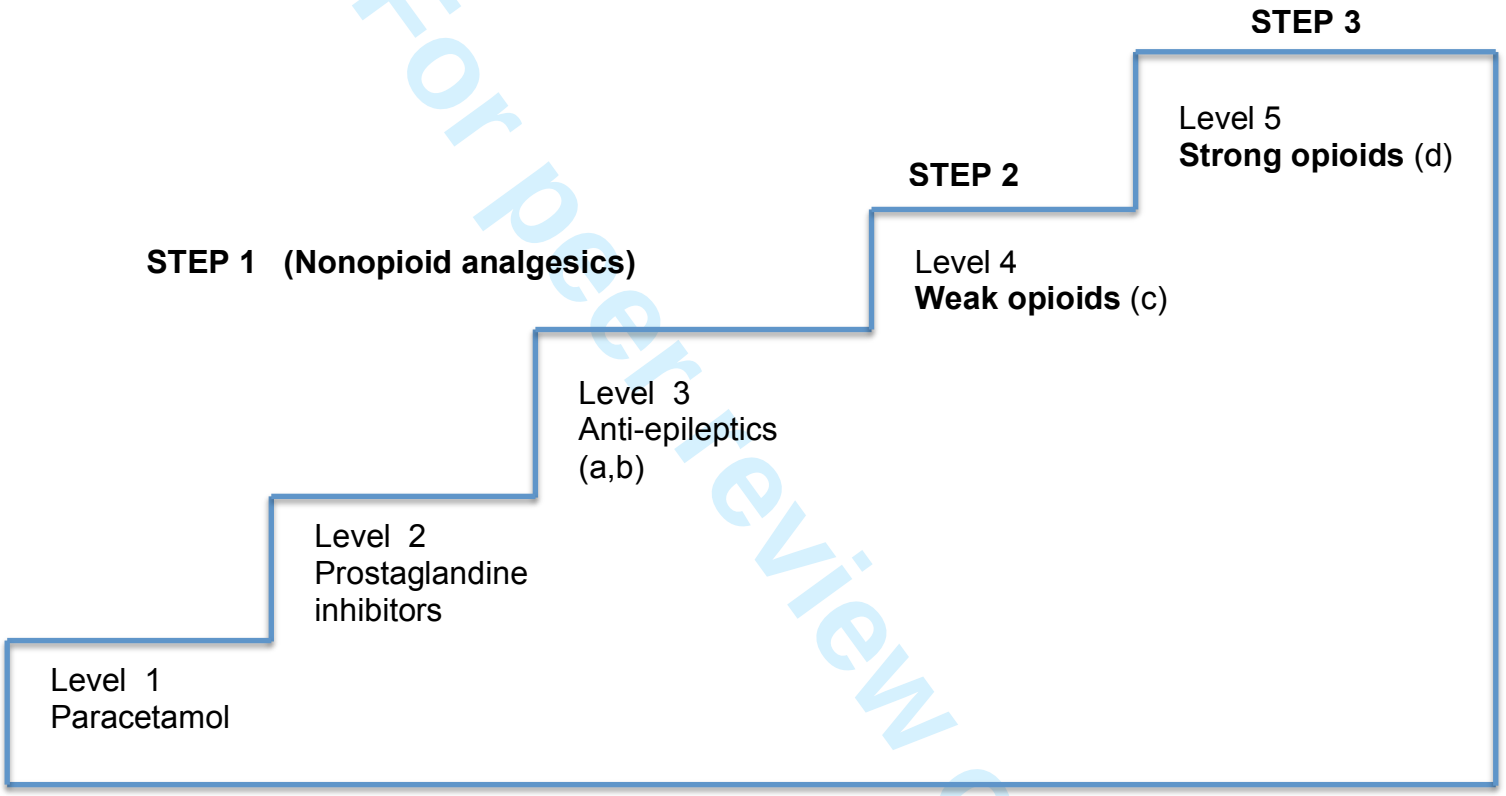
	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found DONE
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported DONE
Objectives	3	State specific objectives, including any prespecified hypotheses DONE
Methods		
Study design	4	Present key elements of study design early in the paper DONE
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection DONE
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up DONE *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable DONE
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group DONE
Bias	9	Describe any efforts to address potential sources of bias DONE
Study size	10	Explain how the study size was arrived at DONE
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why DONE
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding DONE
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed DONE
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram DONE
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders DONE
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) DONE
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time DONE
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included DONE
		(*b*) Report category boundaries when continuous variables were categorized DONE
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives DONE
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias DONE
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence DONE
Generalisability	21	Discuss the generalisability (external validity) of the study results DONE
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based DONE

Time (months)

	period prior to observation						observation period					
	1	2	3	4	5	6	7	8	9	10	11	12
starting patients	no Rx for analgesics						first Rx	Rx - Rx ...				last Rx
continuing patients	first Rx						Rx - Rx - Rx ...					last Rx



Original article

Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in chronic pharmacological pain treatment - a longitudinal population-based study in the Netherlands

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Abstract:

Objective: To examine, in the light of the association between urban environment and poor mental health, whether urbanisation and neighbourhood deprivation are associated with analgesic escalation in chronic pharmacological pain treatment, and whether escalation is associated with prescriptions of psychotropic medication.

Design: Longitudinal analysis of a population-based routine dispensing database in the Netherlands.

Setting: Representative sample of pharmacies, covering 73% of the Dutch nationwide medication consumption in the primary care and hospital outpatient settings.

Participants: 449,410 patients aged 15-85 years were included, of whom 166,374 were in the *Starter group* and 283,036 in the *Continuation group* of chronic analgesic treatment.

Main outcome measure: Escalation of analgesics (i.e. change to a higher level of analgesic potency, classified across five levels) in association with urbanisation (five levels) and dichotomous neighbourhood deprivation analysed over a six-month observation period.

Methods: Ordered logistic multivariate model evaluating analgesic treatment.

Results: In both *Starter* and *Continuation* groups, escalation was positively associated with urbanisation in a dose-response fashion (Starter group: OR (urbanisation level 1 compared to level 5): 1.24; 95% CI 1.18 to 1.30; Continuation group: OR 1.19; 95% CI 1.14 to 1.23). An additional association was apparent with neighbourhood deprivation (Starter group: OR 1.06; 95% CI 1.02 to 1.11; Continuation group: OR 1.04; 95% CI 1.01 to 1.08). Use of somatic and particularly psychotropic co-medication was associated with escalation in both groups.

Conclusion: Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medication prescriptions. These findings suggest that pain outcomes and mental health outcomes share factors that increase risk and remedy suffering.

Introduction

The validity of the well-known epidemiological association between urban environment and mental health[1-3] is supported by work showing that urban living is associated with increased amygdala activity[4], a key region in the regulation of stress, affective experience and pain[5 6]. Pain is the natural comorbid mental experience of somatic conditions[7 8]. In turn, pain is strongly influenced by comorbid common mental disorders particularly affective disorders[9 10]. Given evidence of urban impact on risk for common mental disorders[11], including psychiatric medication prescriptions[12], we hypothesized that pain outcomes, indexed through prescriptions, would be poorer in urban environments and disadvantaged urban neighbourhoods. Pain outcomes were examined at the level of primary care and specialist outpatient care and defined in two ways: (i) escalation of analgesic treatment (i.e. prescription of more potent analgesics) and (ii) co-prescription of psychotropic medication in addition to analgesic treatment.

Objective

We examined the hypothesis that chronic pharmacological pain treatment of hospital outpatients and patients in primary care would show escalation of analgesics in association with the level of urbanisation and neighbourhood index of deprivation. It was predicted that the highest levels of urbanisation and neighbourhood deprivation would be associated with escalation of analgesic treatment to more potent pain medication (e.g. tramadol, morphine, methadone, etc.). Furthermore, we examined the hypothesis that prescriptions of psychotropic medication (e.g. antidepressants, antipsychotics, mood stabilizers, etc.) would

be associated with escalation or de-escalation of analgesics in patients prescribed chronic analgesic treatment. Study hypotheses were specified before inspection of the data.

Method

Data collection

The investigation was carried out by analysing records pertaining to Dutch routine general practice and hospital outpatient treatment settings. Data were obtained from the IMS Health's longitudinal prescription database (Lifelink, affiliate Capelle ad IJssel, The Netherlands)[13]. This data source consists of anonymous longitudinal prescription records from a representative sample of pharmacies and dispensing GPs, covering 73% of the Dutch nationwide medication consumption of outpatients and primary care patients. The computerized *medication-dispensing histories* contain data regarding dispensed medications, type of prescriber, dispensing date, dispensed amount of medication, prescribed dosage, and length of prescription. Data for each patient were anonymously and independently sampled without linkage of prescriptions to the same patient across pharmacies, because patients in the Netherlands are usually loyal to a single pharmacy[14]. Furthermore, research from the Dutch Foundation for Pharmaceutical Statistics (SFK) revealed that in the Netherlands, almost all patients make use of a pharmacy located in their area of living. Eighty-two percent of patients are living in a radius of 3 kilometres from their pharmacy[15]. Potential bias caused by patients getting hospitalized, moving to another address or dying was minimized by studying chronic pharmacological pain treatment, because there were dispensing records for these patients during the whole study period.

Patient groups

Patient selection started with the identification of chronic users of analgesic medication during a six-month prescription period (hereafter: observation period). Chronic use was defined as in receipt of analgesic pharmacotherapy during at least two distinct moments covering an interval of at least two months. In order to track medication for other therapeutic indications (i.e. psychotropic medication and pharmaco-treatment for somatic disorders), patients were observed for a period of six months prior to initiation of analgesic treatment. Next, the cohort with chronic use of analgesics was divided into two groups. *Starters* were defined as patients who had not received any analgesics during the six-month period prior to the observation period (hereafter: *Starter group*). Patients who *continued* with pain medication that was already prescribed in the six month before the observation period formed the second group (hereafter: *Continuation group*). The latter group consisted of all patients who had already received analgesics in the first month of the six-month period prior to the observation period, in order to define chronic analgesic treatment before observation. All data captured a calendar period from May 2008 to September 2009 (Figure 1).

Figure 1: Starter group and Continuation group of chronic analgesic treatment

Insert Figure 1

Legend: Schedule of prescriptions (Rx) in Starter group (top) and Continuation group (bottom) of chronic analgesic treatment covering a 12 month period. Months 7 to 12 are the observation period; months 1 to 6 are the pre-observation period. Patients in the Continuation group received first prescription of analgesics in month 1 of the pre-observation period; there was no follow-up whether analgesics were continued over the entire six-month interval prior to the observation period. The

Starter group did not use any analgesics during the six month interval prior to the observation period.

Data were obtained from the LRx database from month one to twelve as depicted in Figure 1.. Use of other medications (e.g. psychotropic medication and medication for a broad spectrum of somatic conditions) was collected for all patients as well, covering the period of twelve months, consisting of (i) the pre-observation period (month one to six) and (ii) the observation period (month seven to twelve)).

Escalation of pharmacological pain treatment

All individual prescriptions of analgesics were observed for each patient in both the Starter and Continuation groups during the observation period and during the six months prior to the observation period. At each dispensing date, analgesics were classified *a priori* in five levels, in order of analgesic potency (Figure 2). Five escalation levels were provided, based on a minor adaptation of the 3-step WHO-analgesic ladder[16]. Level 5 and 4 are identical to WHO steps 3 (strong opioids) and 2 (weak opioids), respectively. WHO step 1 (non-opioid analgesics) was refined, in order to enable further and clinically relevant differentiation between non-opioid analgesics (level 1: paracetamol, level 2: prostaglandin inhibitors, level 3: anticonvulsants) [16-20]. Furthermore, anti-epileptics were divided in anticonvulsants predominantly prescribed in pain conditions (level 3a: gabapentin and pregabalin) and anticonvulsants with best evidence for epilepsy treatment (level 3b: carbamazepine, valproic acid, lamotrigine)[19-21]. In order to avoid prescription for indications of mood stabilisation or

epilepsy, the latter group was classified at level 3b only if prescribed in combination with analgesic medication at level 1 or 2 (i.e. pain indication) (Figure 2).

Figure 2: 5 levels of analgesic potency, modified from the WHO-analgesic ladder[16]

Insert Figure 2

Legend:

Level 1 (i.e. lowest potency) to level 5 (i.e. highest potency)

(a) Gabapentine, pregabaline in the absence of other anti-epileptic drugs

(b) Carbamazepine, valproic acid, lamotrigine in combination with medication at level 1 or 2

(c) Tramadol, codeine

(d) Methadone, oxycodone, hydromorphone, morphine, buprenorphine, fentanyl, sufentanil, pethidine

Confirmation of escalation was based on the comparison of analgesic potency at the first dispensing day and the last dispensing day within the observation period.

The comparison of first and last prescription of analgesics resulted in the following categories of analgesic escalation: neutral (i.e. no change of analgesic potency), escalation in analgesic treatment (i.e. change to a higher level of analgesic potency), or de-escalation in pharmacological pain treatment (i.e. change to a lower analgesic potency) (Table 1).

If patients received several analgesics on the same day, both the highest and the second highest level of analgesic potency were included in the analyses, in order to define escalation categories (e.g. a change from level 5 plus level 2 to level 5 plus level 3 indicating that escalation had occurred).

Determinants of escalation in analgesic treatment

Three groups of variables hypothesized to act as mediators or confounders were included in the analyses. The first group were patient characteristics such as sex (0=men, 1=women), age (in years) and the location of patient's pharmacy (defined by postal code). The latter variable defined the level of urbanisation following the definition of the Dutch Central Bureau of Statistics (CBS). Conform previous work, and in line with the classification developed by CBS, level of urbanisation was defined by CBS as the number of addresses relative to area surface[22]. Level 1 (i.e. highest level of urbanisation) consists of more than 2500 addresses per square-kilometre (km^2); [level 2 = 1500 to 2500 addresses/km^2, level 3 = 1000 to 1500 addresses/km^2, level 4 = 500 to 1000 addresses/km^2]. Level 5 (i.e. rural environment) consists of less than 500 addresses/km^2; described in more detail elsewhere[23]. More over, neighbourhood deprivation was defined dichotomously (0=no, 1=yes). The dichotomous measure of neighbourhood deprivation was developed by the Netherlands Institute of Research in Healthcare (NIVEL), using socio-economic indicators such as unemployment rate, average income, population density and ethnic variation. On the basis of empirical research in the Netherlands, NIVEL 's neighbourhood deprivation index (NDI) is calculated as follows: NDI = ((ln percentage unemployed people – 3.0236)/0.37706) – ((ln average income – 2.8641)/0.14441) + ((ln population density – 7.0132)/1.06699) + ((ln percentage people of "non-western" ethnicity)/1.11147). NDIs were expressed continuously by NIVEL from low to high. Furthermore, NIVEL defined a dichotomous measure of deprivation at a cut-off of 5.5% (i.e. 885,000 people), in order to assess trends in the proportion of the Dutch population inhabiting an area with the highest NDI and for use in epidemiological research[24]. Healthcare professionals receive higher levels of funding for their services in these deprived areas[25]. Neighbourhood deprivation was associated with

level of urbanisation: 86% of the sample living in deprived neighbourhoods lived in an area with the highest level of urbanisation. The other patients (14%) living in deprived neighbourhoods lived in an area with the second highest level of urbanisation. The majority (76%) of those living in an area of the highest level of urbanisation did not live in a deprived neighbourhood (Table 1).

Table 1: Sample, stratified by Urbanisation and Neighbourhood Deprivation

		Deprived Neighbourhood				% within Deprived Neighbourh.
Type of patient	Urbanisation level	No (patients)	No (%)	Yes (pat.)	Yes (%)	
Starter Group	1	34662	76.3%	10796	23.7%	86.5%
	2	48673	96.6%	1689	3.4%	13.5%
	3	31107	100.0%	0	0.0%	-
	4	28283	100.0%	0	0.0%	-
	5	11164	100.0%	0	0.0%	-
	total	153889	92.5%	12485	7.5%	100.0%
Continuation Group	1	59714	76.2%	18644	23.8%	85.5%
	2	81406	96.3%	3155	3.7%	14.5%
	3	50853	100.0%	0	0%	-
	4	48511	100.0%	0	0%	-
	5	20754	100.0%	0	0%	-
	total	261237	92.3%	21799	7.7%	100.0%
Total Patients		415126	92.4%	34284	7.6%	

Legend: The sample is described in absolute numbers for the Starter and the Continuation group, stratified by living in an urbanised area (level 1 to 5), and a dichotomous measure of neighbourhood deprivation. Furthermore, in the last column, tabulation is presented for living in a deprived neighbourhood as a function of level of urbanisation (e.g. in the Starter group, 86.5% of the sample living in deprived neighbourhoods lived in an area with urbanisation level 1).

Furthermore, psychotropic co-medication was classified into its different classes, and somatic co-medication was similarly grouped in 10 classes (ACE inhibitors, angiotensine II

inhibitors; antidiabetics; beta-blockers; calcium antagonists; functional bowel drugs; laxatives; migraine medication; respiratory medication; steroid-antiphlogistics; stomach protectors) (Table 1 to 3). In the Starting group, occurrence of co-medication was time-coded at three levels according to the day of first occurrence (i.e. co-medication prescription before start with analgesics, at the same day or after start of analgesic treatment) (Table 3). In the Continuation group, occurrence of co-medication was recorded dichotomously (presence/absence), since it was impossible to distinguish occurrence of co-medication as before or at start of analgesic treatment (Table 4).

Statistical analysis

First, we analysed the pattern of (de-) escalation in analgesic treatment by means of an ordered logistic multivariable regression model with adjusted odds ratios (and 95% confidence interval) using SAS version 9 [26]. Statistical significance for the model was defined at conventional alpha of 0.05. The dependent variable in this model was the development of a patient's analgesic treatment (de-escalation, neutral, escalation). Independent variables, entered simultaneously in the model, were demographic characteristics, neighbourhood deprivation, and urbanisation, use of psychotropic medication and use of somatic medication. In the Starter group, we also included first occurrence of co-medication. The modeling strategy was to build, first, a fully saturated model (including all variables), in order to avoid missing relevant information by leaving out non-significant variables. Second, backward elimination was carried out to find the best model fit.

Models for Starter and Continuation groups were run separately, given different sample selection criteria. The ordered logistic multivariable regression model was chosen above the

multinomial model, as the latter does not consider the natural order in our data regarding development of chronic pain treatment, ranging from de-escalation to neutral to escalation. Proportional odds were assumed in the models of escalation and de-escalation of analgesic treatment, and analyses inspected for violation of this assumption. Test on the proportional odds assumption showed significance, which gave us the confidence to use the ordered logistic model. If a determinant was positively associated with escalation of analgesics, absence of this variable was associated negatively with escalation or positively with de-escalation in analgesic treatment (and vice versa). This offered advantage compared to separate models for escalation and de-escalation (such as consistency of model estimates) and avoided double use of patients with a neutral development of analgesic treatment.

Results

Overall, 449,410 patients were included, of which 166,374 were in the Starter group and 283,036 in the Continuation group. The baseline characteristics of both groups are shown in table 2.

Table 2: Baseline characteristics of the patient population with chronic analgesic treatment

		Starter group				Continuation group			
		Deprived Nb.hoods	Urbanicity[1] 1	Urbancity 2-5	Non Depr. Nb.hoods	Deprived Nb. hoods	Urbanicity 1	Urbanicity 2-5	Non Depr. Nb.hoods
Patients	(Absolute)	12485	45458	120916	153889	21799	78358	204678	261237
Change in	Analgesics[2]								
	De-escalation	13.3%	12.1%	10.4%	10.7%	13.2%	12.5%	11.2%	11.4%
	Neutral	70.1%	71.6%	74.5%	74.0%	70.0%	71.4%	73.7%	73.3%
	Escalation	16.5%	16.3%	15.1%	15.3%	16.8%	16.1%	15.1%	15.3%
Gender	Male	39.8%	39.3%	40.3%	40.0%	36.7%	35.2%	34.6%	34.6%
	Female	60.2%	60.7%	59.7%	60.0%	63.3%	64.8%	65.4%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	6.4%	1.8%	1.6%	1.8%	1.7%
	26-40	23.8%	19.2%	16.3%	16.6%	14.0%	10.8%	9.7%	9.7%
	41-65	50.0%	49.6%	50.9%	50.6%	56.9%	53.4%	51.8%	51.9%
	65-85	19.8%	25.2%	26.2%	26.4%	27.3%	34.2%	36.7%	36.7%
First	Analgesics								
	Level 1	3.2%	3.9%	4.0%	4.0%	3.0%	3.8%	4.1%	4.1%
	Level 2	64.8%	66.6%	72.6%	71.4%	47.8%	47.1%	53.6%	52.1%
	Level 3	2.2%	2.5%	2.6%	2.6%	6.4%	8.1%	8.9%	8.8%
	Level 4	27.4%	24.2%	18.3%	19.3%	36.1%	33.9%	27.6%	28.8%
	Level 5	2.4%	2.9%	2.6%	2.7%	6.8%	7.2%	5.9%	6.2%
	level 4/5	29.8%	27.0%	20.8%	21.9%	42.8%	41.1%	33.5%	35.0%
Last	Analgesics								
	Level 1	3.4%	3.9%	4.0%	4.0%	3.4%	4.1%	4.3%	4.3%
	Level 2	61.9%	63.0%	68.4%	67.4%	44.5%	44.1%	50.1%	48.8%
	Level 3	3.0%	3.3%	3.4%	3.4%	7.0%	8.4%	9.2%	9.1%
	Level 4	27.6%	24.6%	18.9%	19.9%	36.8%	34.5%	28.4%	29.6%
	Level 5	4.1%	5.2%	5.3%	5.3%	8.3%	9.0%	7.9%	8.2%
	Level 4/5	31.7%	29.8%	24.2%	25.2%	45.1%	43.4%	36.3%	37.7%
Concomitant	Medication[3]								
	Any concomitant medication	78.8%	79.0%	77.3%	77.7%	89.3%	89.6%	88.0%	88.4%
	Migraine medication	3.9%	3.6%	3.8%	3.7%	5.9%	5.2%	5.1%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	35.3%	51.6%	53.2%	50.2%	51.0%
	Sedatives	27.0%	29.0%	27.4%	27.9%	41.5%	43.4%	40.6%	41.4%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.3%	0.4%	0.4%	0.4%
	Antipsychotics total	4.1%	3.9%	3.1%	3.2%	6.7%	6.1%	4.9%	5.1%
	Antipsychotics 2nd generation	2.4%	2.2%	1.5%	1.6%	4.1%	3.5%	2.5%	2.7%
	Antipsychotics classic	2.0%	2.1%	1.8%	1.8%	3.2%	3.2%	2.7%	2.8%
	Bupropion	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%
	TCA	5.2%	5.0%	5.0%	5.0%	9.5%	9.4%	9.6%	9.6%
	Other antidepressants[4]	2.4%	2.0%	1.6%	1.7%	4.0%	3.3%	2.7%	2.8%
	SNRI	2.6%	2.4%	2.2%	2.2%	4.5%	4.0%	3.5%	3.6%
	SSRI	7.5%	7.0%	6.4%	6.5%	10.3%	10.0%	9.0%	9.2%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.5%	0.3%	0.5%	0.4%	0.5%
	Any somatic medication	72.3%	72.6%	71.0%	71.4%	83.0%	82.9%	81.7%	81.9%
	Cardiovascular medication[5]	30.9%	31.4%	30.8%	30.9%	35.2%	34.9%	34.9%	34.9%
	Other Somatic medication[6]	65.2%	65.5%	64.0%	64.3%	76.9%	76.7%	75.4%	75.6%

Legend: Patient characteristics are presented as percentages (e.g. age, gender, level of analgesic treatment, change in analgesic treatment (e.g. escalation, de-escalation, and neutral development of prescriptions), and concomitant medication). Absolute patient numbers are presented for the Starter and the Continuation group of chronic analgesic treatment concerning level of urbanicity and for neighbourhood deprivation.

(1) Urbanicity = Urbanisation (level 1 = highest level of urbanisation; level 5 = rural environment)

~~(1)~~(2) Change in pain medication from first to last prescription (neutral = no change in level of potency, escalation = change to a higher level of analgesic potency, de-escalation = change to lower analgesic potency)

~~(1)~~(3) Concomitant drug use, observed during a period of 12 month

(4) Other than Bupropion, MAO inhibitors, SNRI, SSRI, and TCA

(5) Cardiovascular medication: beta-blocker, calcium antagonist, ACE inhibitor, angiotensine II inhibitor

(6) Gastro-intestinal medication: anti-diabetics, steroid-antiphogistics, respiratory medication

About 7.6% of all escalating patients were residing in a deprived neighbourhood, and approximately 27.6% were living in an area of the highest level of urbanisation (level 1) (Table 2). The majority were female, and there were more patients showing escalation (15.4%) than de-escalation (11.3%) of analgesic treatment. The majority of patients continued a neutral analgesic treatment regime (73.3%) (Table 2). Most of the patients were treated at level 2 or level 4 of analgesic potency. Almost all patients were using other medications, regardless of the different categories in table 2 (84.5%). Around half were using psychotropic medication (45.2%), most were using somatic co-medication (78.1%), and more than a third were using both (38.8%) (Table 2).

The Starter group mainly initiated an analgesic at level 2 (70.9%) and level 4 (19.9), whereas only 2.6% directly initiated at level 5. However, analgesic potency level 4 and 5 increased up to 20.5% respectively 5.2% by the time of the last prescription in the Starter group (Table 2).

In the Continuation group, patients already received analgesics at a higher level of potency at inclusion compared to the last observed level of medication potency in the Starter group. Level 4 and 5 was observed in 35.6% at the start of the observation period, increasing to 38.3% at the end of observation period (Table 2).

Escalation of analgesic treatment was observed more often in deprived neighbourhoods and in areas of the highest levels of urbanisation (16.8% and 16.1% in the Continuation group, respectively 16.5% and 16.3% in the Starter group) compared to rural areas (15.1%) and non-deprived neighbourhoods (15.3.%) (Table 2). The proportion of patients with neutral development of analgesic treatment was lower in deprived neighbourhoods and areas with the highest degree of urbanisation compared to less densely populated areas (Table 2).

In the Starter group, escalation was positively associated with lower level of first observed pain medication (highest adjusted Odds Ratio (OR) 58.23 at analgesic level 1; 95% Confidence Interval (CI) 53.60 to 63.27; lowest OR 1.36 at analgesic level 4; 95% CI 1.27 to 1.45; compared to reference level 5) (Table 3). Escalation was furthermore associated, in a dose-response fashion, with level of urbanisation (highest adjusted OR 1.24 at urbanisation level 1; 95% CI 1.18 to 1.30; compared to reference level 5) (Table 3). Furthermore, a weak but additional association existed between escalation and neighbourhood deprivation (OR 1.06; 95% CI 1.02 to 1.11) (Table 3). Use of tricyclic antidepressants (TCA), mood stabilizers (OR 1.36; 95% CI 1.07 to 1.42), sedatives, cardiovascular medication (OR 1.16; 95% CI 1.13 to 1.19) and medications for other somatic conditions was associated with analgesics escalation, when prescribed *before* start of analgesics (Table 3). Similarly, in the Starter group, escalation of analgesic treatment was also associated with the use of selective

noradrenalin serotonin reuptake inhibitors (SNRI), sedatives (OR 1.82; 95% CI 1.74 to 1.89), TCA (OR 2.19; 95% CI 2.03 to 2.36), and antipsychotics (OR 2.43; 95% CI 2.19 to 2.68) when prescribed *after* start of analgesics (Table 3). Negative associations with escalation (i.e. positive association with de-escalation) were apparent for younger age, female sex, and pharmacological migraine treatment. Furthermore, use of antipsychotics was negatively associated with escalation if started *simultaneously* with analgesic treatment (OR 0.70; 95% CI 0.58 to 0.84) (Table 3).

The use of selective serotonin reuptake inhibitors (SSRI), before, at or after start of analgesic treatment was not associated with escalation of analgesics in the Starter group (Table 3).

In the Starter group, the original fully saturated model and the model after backward elimination revealed the same variables associated significantly with escalation in chronic pharmacological pain treatment (Table 3).

Table 3: Associations with escalation in pharmacological pain treatment for the *Starter group* of chronic analgesic treatment

Exposure		Adj. Odds Ratio	95%	CI[1]
			Lower	Upper
Analgesics[2]	Level 1	58.23	53.60	63.27
	Level 2	17.92	16.75	19.16
	Level 3	4.66	4.23	5.14
	Level 4	1.36	1.27	1.45
	Level 5	Reference	-	-
Gender	Female	0.97	0.95	0.99
	Male	Reference	0.00	0.00
Age (years)	15-25	0.73	0.69	0.77
	26-40	0.81	0.78	0.84
	41-65	0.87	0.85	0.90
	66-85	Reference	-	-
Urbanisation[3]	1	1.24	1.18	1.30
	2	1.16	1.11	1.22
	3	1.11	1.06	1.17
	4	1.07	1.02	1.13
	5	Reference	-	-
Deprived	Yes	1.07	1.02	1.11
Neighbourhood	No	Reference	-	-
SNRI	Before start of analgesics[4]	1.05	0.96	1.14
	Same start date	1.28	0.97	1.69
	After analgesics started	1.26	1.09	1.45
	None	Reference	-	-
SSRI	Before start of analgesics	0.97	0.92	1.02
	Same start date	0.97	0.83	1.15
	After analgesics started	1.07	0.97	1.18
	None	Reference	-	-
TCA	Before start of analgesics	1.23	1.15	1.32
	Same start date	1.32	1.12	1.54
	After analgesics started	2.19	2.03	2.36
	None	Reference	-	-
Other AD	Before start of analgesics	1.03	0.93	1.15
	Same start date	0.93	0.71	1.21
	After analgesics started	1.22	1.06	1.42
	None	Reference	-	-
Antipsychotics	Before start of analgesics	0.92	0.85	1.01
	Same start date	0.69	0.58	0.83
	After analgesics started	2.42	2.18	2.67
	None	Reference	-	-
Mood stabilizers	Before start of analgesics	1.40	1.10	1.79
	Same start date	0.91	0.43	1.89
	After analgesics started	0.71	0.39	1.31
	None	Reference	-	-
Sedatives	Before start of analgesics	1.24	1.20	1.28
	Same start date	1.25	1.18	1.33
	After analgesics started	1.82	1.74	1.89
	None	Reference	-	-
Cardio-Vascular drugs	Before start of analgesics	1.16	1.13	1.19
	Same start date	0.86	0.79	0.95
	After analgesics started	1.35	1.26	1.45
	None	Reference	-	-
Other Somatic drugs	Before start of analgesics	1.25	1.22	1.29
	Same start date	1.11	1.07	1.15
	After analgesics started	1.19	1.15	1.23
	None	Reference	-	-
Migraine medication	Before start of analgesics	0.83	0.77	0.89
	Same start date	0.95	0.78	1.17
	After analgesics started	0.91	0.81	1.02
	None	Reference	-	-

Legend:
(1) 95% CI: confidence interval
~~(1)~~(2) Escalation = change to a higher level of analgesic potency, level 5 = highest level
(3) 1 = highest level of urbanisation, 5 = rural environment
(4) Starting date of medication (before, at the same day or after start of analgesics)

In the Continuation group, escalation of analgesics was positively associated with lowest levels of first observed analgesics (highest adjusted OR 16.00 at analgesic level 1; 95% CI 15.20 to 16.85; lowest OR 1.55 at analgesic level 4; 95% CI 1.50 to 1.61; compared to reference level 5) (Table 4). Furthermore, escalation was associated with level of urbanisation in a dose response fashion (highest adjusted OR 1.19 at level 1; 95% CI 1.14 to 1.23; compared to reference level 5) (Table 4). There was also an association between escalation and deprived neighbourhoods, use of SSRI, SNRI, TCA, all antipsychotics, and sedatives (OR 1.31; 95% CI 1.29 to 1.33) as well as use of somatic co-medication (OR 1.12; 95% CI 1.10 to 1.14) (Table 4). De-escalation was associated with female sex, younger age, treatment of migraine, and use of second-generation antipsychotics (OR 0.80; 95% CI 0.70 to 0.91) (Table 4).

The saturated model showed that 22 out of 29 variables had significant associations. All these variables remained significant in the backward elimination approach. One additional variable displayed a significant association after backward elimination: 'TCA high dosage'. The OR's did not (16 variables), or only minimally (6 variables) differ between the fully saturated model and the backward elimination model. The only variable showing a degree of difference was 'TCA total' (fully saturated model: OR = 1.19 (CI: 1.06 – 1.32); backward elimination model: OR = 1.33 (CI: 1.29 – 1.36)) (Table 4).

Table 4: Associations with escalation in pharmacological pain treatment for the *Continuation group* of chronic analgesic treatment

Exposure		Adjusted Odds Ratio	95% CI[1] Lower	Upper
Analgesics[2]	Level 1	16.00	15.20	16.85
	Level 2	7.87	7.59	8.16
	Level 3	3.14	3.00	3.28
	Level 4	1.55	1.50	1.61
	Level 5	Reference	-	-
Gender	Female	0.96	0.94	0.98
	Male	Reference	-	-
Age (years)	15-25	0.91	0.85	0.97
	26-40	0.98	0.95	1.01
	41-65	0.99	0.97	1.01
	66-85	Reference	-	-
Urbanisation[3]	1	1.18	1.14	1.23
	2	1.14	1.10	1.17
	3	1.08	1.04	1.12
	4	1.05	1.01	1.09
	5	Reference	-	-
Deprived Neighbourhood	Yes	1.04	1.01	1.08
	No	Reference	-	-
SNRI		1.19	1.02	1.40
SSRI		1.03	1.004	1.07
TCA[4]		1.19	1.06	1.32
Other AD		1.08	1.03	1.14
Antipsychotics	Total	1.24	1.08	1.43
	1st generation	1.01	0.88	1.15
	2nd generation	0.80	0.70	0.91
Mood stabilizers		0.97	0.85	1.10
Sedatives		1.31	1.29	1.34
Migraine		0.95	0.91	0.99
Cardio Vascular Drugs		1.12	1.10	1.14
Other Somatic Drug classes		1.12	1.10	1.14

Legend:
(1) 95% CI: confidence interval
(2) Escalation = change to a higher level of analgesic potency, level 5 = highest level
(3) 1 = highest level of urbanisation, 5 = rural environment
(4) TCA total (fully saturated model: OR = 1.19 (CI: 1.06 – 1.32); BWE model: OR = 1.33 (CI: 1.29 – 1.36))

Over time, the escalation process continues even after the first 6 months of chronic analgesic treatment. In the Starter group, opioid-analgesics (level 4/5) were dispensed in 29.8% of patients living in a deprived neighbourhood. In contrast, 42.8% of patients in deprived neighbourhoods used opioids in the Continuation group, after one year of prescription. A similar, but attenuated development was seen at urbanisation level 1 and level 2 to 5 (Table 2).

Discussion

Escalation of chronic analgesic treatment was observed more often in urban areas and deprived neighbourhoods within urban areas, suggesting pain outcomes either are associated with individual characteristics that are more prevalent in urban and deprived areas, or subject to contextual influences, like area-level stress or social fragmentation, regardless of individual level characteristics. One individual level variable that may explain part of the association with urbanicity and deprivation is socio-economic status[27 28], which was not available for inclusion in the model. Nevertheless, the fact that the association with urbanicity remained with deprivation adjusted for in the same model, suggests that urban effects may not be reducible entirely to individual-level socio-economic status. Furthermore, although neighbourhood deprivation and urbanicity are correlated, additional association of deprivation with escalation of analgesics exists over and above urbanisation, indicating that other parameters than population density are involved too. However, the findings could also be attributed to reverse causation, i.e. patients with worsening pain may move into more urban and deprived neighbourhoods as a consequence of being disabled due to ill health. ~~Although unlikely to entirely explain the current findings, it cannot be excluded.~~

Regardless of the underlying mechanism, results clearly echo findings of un-confounded higher rates of poor mental health in areas of higher levels of urbanisation and greater neighbourhood deprivation[11 29], and suggest that the outcome of mental disorder comorbidity associated with somatic disorders may show similar predictable variation. Functional pain syndromes and psychiatric disorders show high levels of interdependency[30-35], and psychiatric conditions enhance severity of somatic symptoms[36]. Thus, part of the mechanism underlying the association between pharmacological pain escalation and urban environment may be explained by urbanisation increasing the risk for mental ill health. This

hypothesis is supported by the findings, as in both the Starter and the Continuation groups, escalation of chronic analgesic treatment was associated not only with urban environment and neighbourhood deprivation, but also with prescription of various psychotropic medications prescribed in association. In general, the positive association of escalating analgesic treatment with psychotropic medication was as strong or even stronger than the association with prescribed somatic co-medication, with the exception of the observed de-escalating effect, in the Continuation group, of second-generation antipsychotics, which possess powerful analgesic properties[37 38]. This is accordance with the literature, given the fact that psychiatric conditions can enhance symptom severity in somatic patients[36], which sometimes may impact even more that the somatic condition itself[39].

Although the absolute difference between analgesic escalation in the urban vs. less urban environment was small, this difference may be relevant from a public health perspective, given the high rate of painful conditions in the general population. Furthermore, prevention of persistent pain states is relevant with regard to costs[40]. Given the well known increase of health care costs in complex patients with frequent utilization of health care, with or with out psychiatric comorbidity, only a small number of patients is required to cause relevant clinical cost changes[41]. A more effective treatment of persistent pain, including treatment of psychiatric comorbidity, may have a cost-saving effect. Targeting populations with painful conditions for early recognition and treatment of mental health problems may not only be cost-effective from a public health perspective, but also represent an area of considerable unmet clinical need, since opioid escalation is an inflationary development in the treatment of painful conditions [42 43]. Moreover, broadening the pain agenda to a better understanding of associated mental health problems could minimize failed surgery outcomes, for example in patients with undetected mental

disorders. For instance, new surgical procedures were found to be more common in chronic back pain (CBP) patients with Post-traumatic Stress Disorder compared to CBP patients without[44]. Similarly, depression was demonstrated in 47.4 % of patients with low back pain who had no surgery, in 50% of those with one surgical procedure, and in 62.5 % of those who had undergone surgery more than once[45]. Influencing central pain sensitization by providing adequate antidepressant treatment in depressive conditions may help prevent surgical escalation.

Odds ratios for escalation of analgesics in relation to original level of analgesics may represent ceiling effects in both starter and continuation groups - patients already at level 5 have nowhere stronger to go; treatment of patients at level 1 at baseline can escalate to stronger medication. Ceiling effects may reflect the pattern of prescribing analgesics in general practice. Given these, it has been suggested that the WHO analgesic ladder is in need of updating[46]. For example, Vargas-Schaffer is broadening the ladder with a 4th surgical step; in the current article, however, we guide attention to treatment aspects related to underestimated mental disorder comorbidity in persistent pain states.

The speculative question remains to what degree escalation of analgesic treatment and its association with psychotropic medication reflects therapeutic paradigms to remedy pain, treatment of psychiatric comorbidity, or a cause of psychopathology. For instance, in the Starter and the Continuation group of chronic analgesic treatment, escalation of analgesics was consistently and positively associated with the use of TCA. This prescription habit may reflect routine off-label paradigms in the pharmacological treatment of pain syndromes[10 47-49]. However, given the evidence regarding TCA's efficacy in pain conditions, negative rather than positive associations with escalation of analgesics should have been

expected. More likely, since the association with TCAs was as strong as the association of sedatives with analgesic escalation, it may be a reflection of affective or addictive comorbidity in persistent pain, for example in vulnerable cases of opiate-induced sensitization, tolerance and hyperalgesia[50-56]. Our data indicate that escalation of analgesics may represent an ongoing process after even months of treatment, which occurs not exclusively in the context of environmental deprivation. Since prescriptions of psychotropic and (attenuated) somatic medication show a similar pattern over time, escalation may also be driven to a degree by patient factors such as opioid tolerance, opioid-induced hyperalgesia[53], or disease progression.

Given the literature on this topic[47-51 57], negative associations of particularly antidepressants with escalation of chronic analgesic treatment would have been expected. Nevertheless, negative associations between escalation of chronic analgesic treatment were also found, for example with migraine treatment (Tables 3 and 4). Moreover, the use of antipsychotics was negatively associated with analgesic escalation in the Starter group - if prescribed after start of analgesic treatment. In the Continuation group, de-escalation was specifically associated with the use of second-generation antipsychotics. This outcome is interesting and deserves further investigation, given that limited evidence for the efficacy of antipsychotics in pain conditions already exists[37 38].

The results of the current study should be seen in the light of several limitations. The use of routine data rather than a targeted data collection could have caused more random error resulting in type II error. Unidentified confounding may have played a role, as randomization was not possible and pre-post designs are sensitive to effects of unmeasured changes affecting outcome measures over time. Another limitation is the lack of outcomes

other than urbanisation, psychotropic medication or somatic co-medication. For instance, there were no estimates regarding care consumption or illness-related sick leave. Changes in patient-related outcomes like illness severity, global functioning, quality of life and treatment satisfaction should also form part of prospective evaluations. The type of data used is subject to the possibility of ecological fallacy: people whose pharmacy is in a deprived or urban neighbourhood do not necessarily experience that level of deprivation or urbanicity. Furthermore, this study only collected data over a twelve-month period. Affect and pain monitoring deserves longer evaluation. Finally, due to the study design, associations do not allow for causal inference.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Numerous observational studies have observed higher rates of poor mental health in urban and deprived neighbourhood environments.

Pain syndromes and mental disorders show high levels of interdependency, and mental disorders are known to enhance severity of somatic symptoms.

WHAT THIS STUDY ADDS

Escalation of chronic analgesic treatment in persistent pain is associated with urban environments and deprived neighbourhoods, and occurs in a context of increased levels of psychotropic medication prescribing, suggesting persistent pain outcomes are associated with area influences affecting mental health.

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in collaboration with CL, JvO, and JS. CL and JvO drafted the paper. All authors contributed to subsequent drafts of the paper, including the final version. JvO is guarantor.

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Reply to reviewer's comments regarding Manuscript ID BMJopen-2011-000731.R1 entitled "Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in chronic pharmacological pain treatment - a longitudinal population-based study in the Netherlands" (after reviewer's recommendation for publication).

Changes in the original manuscript are marked with "track changes".

Reviewer Udo Reulbach

The authors have responded sufficiently to all my queries. I have no further comments. From my point of view, the quality of the article has greatly improved.

Reviewer A.K. Mantel-Teeuwisse

-The manuscript has been improved by the clarifications given and changes made by the authors. In my view, the paper still lacks sufficient focus, especially in the discussion section. It is clear that the authors advocate to "broaden the pain agenda to an understanding that includes mental health perspectives". However, at least I missed a clear and concise link with the aim of this study – to assess whether the level of urbanization and neighbourhood deprivation are associated with analgesic escalation.

One may hypothesise that mental illness comes into play, but this has not been studied as such in detail. For example, the authors conclude "Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medications, suggesting pain outcomes in part reflect area influences affecting mental health." I am not sure the last part of this sentence can be concluded from the presented data. The increased risk of escalation when using psychotropic medication is an independent risk, adjusted for many factors including level of urbanization and neighbourhood deprivation. Similarly, both urbanization and neighbourhood deprivation are independently associated with escalation as well (although I am not sure the remark by Dr Kirkbride about the high correlation between these two has been sufficiently addressed). But this does not necessarily mean that low level of urbanization and neighbourhood deprivation lead to use of psychotropic medication (as a proxy for mental illness) which then leads to dose escalation. Maybe I am missing the point here; I would be happy if the authors could further share their thoughts on this.

Reply: We agree this needs further clarification. Our argument was based not only on the independent risks linking urban environment and escalation on the one hand and psychotropic medication and escalation on the other, but also on published findings on links between urban environment and mental health on the one hand and urban environment and use of psychotropic medication on the other (Peen J, Schoevers RA, Beekman AT, et al. The current status of urban-rural differences in psychiatric disorders. *Acta Psychiatr Scand* 2010;121(2):84-93. Crump C, Sundquist K, Sundquist J, et al. Neighborhood deprivation and psychiatric medication prescription: a Swedish national multilevel study. *Ann Epidemiol*;21(4):231-7.). Given these findings, the abstract conclusion now reads as follows: "**Escalation of chronic analgesic treatment is associated with urban and deprived environments, and occurs in a context of adding psychotropic medication prescriptions.**

These findings suggest that pain outcomes and mental health outcomes share factors that increase risk and remedy suffering".

-I am also still a bit puzzled by the definition of "continuous use". I now understand that the authors wish to compare starters with those who have started 6 months earlier. Did all of the continuous users use analgesics during the whole period of six months prior to the observation period? If that was a requirement (I suppose so), it may be helpful to amend Figure 1 to reflect this use during all of these months.

Reply: In order to ensure comparability, we measured analgesics' escalation during an interval of the same length for the Starter and the Continuation group. Regarding "continuous use", yes, we wished to compare starters with those who had started analgesic treatment six months earlier. No, we did not follow up whether the Continuation group used analgesics over the entire six month interval prior to the observation period. The Starter group, however, did not use any analgesics during the six month interval prior to the observation period. Technically, we could have measured escalation of continuing patients over a longer time interval, but then the definition of escalation between both groups would be different and a direct comparison of starters and continuing patients would have become difficult.
We added the following text to the legend of Figure 1: "**Patients in the Continuation group received first prescription of analgesics in month 1 of the pre-observation period; there was no follow-up whether analgesics were continued over the entire six-month interval prior to the observation period. The Starter group did not use any analgesics during the six month interval prior to the observation period**".

-Table 2: I do understand that the authors need to make some choices in which data to present. However, I feel that the main study outcome, % of escalation, neutral or de-escalation is now a bit "hidden" in table 2. The justification for comparing level 1 with levels 2-5 is still lacking (why not another combination?). Ideally, these % would therefore be presented for each level and for neighbourhood deprivation yes/no. In the current table, % is not displayed for those not living in a deprived neighbourhood, which hampers proper interpretation of the % escalation in deprived neighbourhoods.

Reply: We added a column % of escalation in "non deprived neighbourhoods" to Table 2. Given the small difference with column "urbanicity level 2-5" our choice to summarize levels of urbanisation is justifiable. Please note that we had to make choices regarding data presentation in order to guarantee overview and to avoid diluted results. In our opinion, this table now makes for comfortable reading, without withholding any relevant information.
Thus, table 2 now reads:
(On the following page)

		Starter group				Continuation group			
		Deprived Nb.hoods	Urbanicity[1] 1	Urbancity 2-5	Non Depr. Nb.hoods	Deprived Nb. hoods	Urbanicity 1	Urbanicity 2-5	Non Depr. Nb.hoods
Patients	(Absolute)	12485	45458	120916	153889	21799	78358	204678	261237
Change in	Analgesics[2]								
	De-escalation	13.3%	12.1%	10.4%	10.7%	13.2%	12.5%	11.2%	11.4%
	Neutral	70.1%	71.6%	74.5%	74.0%	70.0%	71.4%	73.7%	73.3%
	Escalation	16.5%	16.3%	15.1%	15.3%	16.8%	16.1%	15.1%	15.3%
Gender	Male	39.8%	39.3%	40.3%	40.0%	36.7%	35.2%	34.6%	34.6%
	Female	60.2%	60.7%	59.7%	60.0%	63.3%	64.8%	65.4%	65.4%
Age (years)	15-25	6.3%	6.1%	6.5%	6.4%	1.8%	1.6%	1.8%	1.7%
	26-40	23.8%	19.2%	16.3%	16.6%	14.0%	10.8%	9.7%	9.7%
	41-65	50.0%	49.6%	50.9%	50.6%	56.9%	53.4%	51.8%	51.9%
	65-85	19.8%	25.2%	26.2%	26.4%	27.3%	34.2%	36.7%	36.7%
First	Analgesics								
	Level 1	3.2%	3.9%	4.0%	4.0%	3.0%	3.8%	4.1%	4.1%
	Level 2	64.8%	66.6%	72.6%	71.4%	47.8%	47.1%	53.6%	52.1%
	Level 3	2.2%	2.5%	2.6%	2.6%	6.4%	8.1%	8.9%	8.8%
	Level 4	27.4%	24.2%	18.3%	19.3%	36.1%	33.9%	27.6%	28.8%
	Level 5	2.4%	2.9%	2.6%	2.7%	6.8%	7.2%	5.9%	6.2%
	level 4/5	29.8%	27.0%	20.8%	21.9%	42.8%	41.1%	33.5%	35.0%
Last	Analgesics								
	Level 1	3.4%	3.9%	4.0%	4.0%	3.4%	4.1%	4.3%	4.3%
	Level 2	61.9%	63.0%	68.4%	67.4%	44.5%	44.1%	50.1%	48.8%
	Level 3	3.0%	3.3%	3.4%	3.4%	7.0%	8.4%	9.2%	9.1%
	Level 4	27.6%	24.6%	18.9%	19.9%	36.8%	34.5%	28.4%	29.6%
	Level 5	4.1%	5.2%	5.3%	5.3%	8.3%	9.0%	7.9%	8.2%
	Level 4/5	31.7%	29.8%	24.2%	25.2%	45.1%	43.4%	36.3%	37.7%
Concomitant	Medication[3]								
	Any concomitant medication	78.8%	79.0%	77.3%	77.7%	89.3%	89.6%	88.0%	88.4%
	Migraine medication	3.9%	3.6%	3.8%	3.7%	5.9%	5.2%	5.1%	5.1%
	Any psychotropic medication	35.1%	36.6%	34.8%	35.3%	51.6%	53.2%	50.2%	51.0%
	Sedatives	27.0%	29.0%	27.4%	27.9%	41.5%	43.4%	40.6%	41.4%
	Mood stabilizers	0.2%	0.3%	0.2%	0.3%	0.3%	0.4%	0.4%	0.4%
	Antipsychotics total	4.1%	3.9%	3.1%	3.2%	6.7%	6.1%	4.9%	5.1%
	Antipsychotics 2nd generation	2.4%	2.2%	1.5%	1.6%	4.1%	3.5%	2.5%	2.7%
	Antipsychotics classic	2.0%	2.1%	1.8%	1.8%	3.2%	3.2%	2.7%	2.8%
	Bupropion	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%
	MAO inhibitors	0.0%	0.0%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%
	TCA	5.2%	5.0%	5.0%	5.0%	9.5%	9.4%	9.6%	9.6%
	Other antidepressants[4]	2.4%	2.0%	1.6%	1.7%	4.0%	3.3%	2.7%	2.8%
	SNRI	2.6%	2.4%	2.2%	2.2%	4.5%	4.0%	3.5%	3.6%
	SSRI	7.5%	7.0%	6.4%	6.5%	10.3%	10.0%	9.0%	9.2%
	Psycho-stimulants	0.4%	0.5%	0.5%	0.5%	0.3%	0.5%	0.4%	0.5%
	Any somatic medication	72.3%	72.6%	71.0%	71.4%	83.0%	82.9%	81.7%	81.9%
	Cardiovascular medication[5]	30.9%	31.4%	30.8%	30.9%	35.2%	34.9%	34.9%	34.9%
	Other Somatic medication[6]	65.2%	65.5%	64.0%	64.3%	76.9%	76.7%	75.4%	75.6%

-Tables 3-4: If the editor agrees I would prefer to present unadjusted ORs as well.

Reply: Of course we remain open to editorial advice in this issue. As we stated earlier, we decided to leave out crude ORs, as in our view they do not add information since they're not corrected for coincidental variation in the other variables. Given the already large amount of figures/tables, and the amount of information that would need to be added, we refrained from adding non-vital information. With regard to the complexity of the tables, as mentioned earlier by reviewer Mantel-Teeuwisse and Reulbach, our aim is to guarantee overview and readability.

-The absolute risk difference of (approximately) 1.5% in escalation between different levels of urbanicity would mean that for every 67 patients treated with analgesics, 1 additional escalation would be expected in the lowest level of urbanicity as compared to levels 2-5. One may indeed argue that this is important from a public health perspective. The discussion of the clinical implications of this finding could be a bit more focused in my opinion. The authors now directly assume that this is due to mental illness and elaborate on that (e.g. page 21, lines 46 and further). But I am not completely convinced this can be concluded – see comment above – and would therefore refrain from too much elaboration in that direction.

Reply: Given the well-known increase of health care costs in complex patients with frequent utilization of health care, with or with out psychiatric comorbidity, only a small number of patients is required to cause relevant clinical cost changes (de Jonge P, Huyse FJ, Stiefel FC. Case and Care Complexity in the Medically Ill. *Med Clin N Am* 2006;90:679-92.). Thus, even without psychiatric comorbidity, escalation of analgesics in chronic pain states is of clinical relevance.

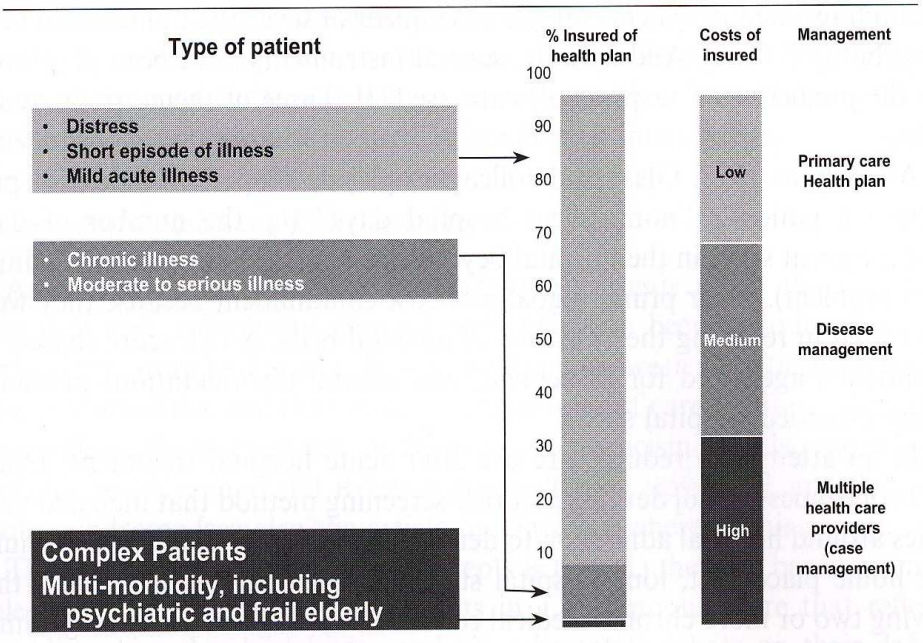

Fig. 1. Matching levels of case complexity to complexity of care in the management of the medically ill.

Adapted from de Jonge et al. *Med Clin N Am* 2006.

Regarding somatic and psychiatric multi-morbidity, please see our reply above on first comment of reviewer Mantel-Teeuwisse.

We added a sentence to the discussion (page 21, lines 13 to 16 of the original manuscript): "**Given the well known increase of health care costs in complex patients with frequent utilization of health care, with or with out psychiatric comorbidity, only a small number of patients is required to cause relevant clinical cost changes[41]**".

Reviewer James B Kirkbride

1. P9, line 7-9: the new sentence beginning "Urbanisation is defined by CBS…" does not read correctly in English after the comma, and should be corrected.

Reply: P9, original manuscript line 6-8 reads correctly in English now: "**Conform previous work, and in line with the classification developed by CBS, level of urbanisation was defined as the number of addresses relative to area surface[22]**".

2. Neighbourhood Deprivation Index – thank you for providing the additional information about this variable. However, I am unsure of the utility of using this variable in your analysis. This dichotomized variable only distinguishes between the upper most deprived neighbourhoods (5.5%) and the remainder. It would be preferable to use the raw scores from NIVEL, rather than this dichotomous variable. Furthermore, the NDI includes population density in it as a measure, which means your urbanicity and deprivation variables are likely to be highly correlated.

Reply: Unfortunately, as we stated in the reply to reviewers' comments regarding Manuscript ID BMJopen-2011-000731 (03-May-2012), we do not have raw NDI scores from NIVEL. Although neighbourhood deprivation and urbanicity are correlated, additional association of deprivation with escalation of analgesics exists over and above urbanisation, indicating that other parameters than population density are involved too.
We added a sentence to the discussion (page 20, lines 10 to 13 of the original manuscript): "**Furthermore, although neighbourhood deprivation and urbanicity are correlated, additional association of deprivation with escalation of analgesics exists over and above urbanisation, indicating that other parameters than population density are involved too**".

3. Table 1 – the presentation of the data in this table is very unclear. I cannot see easily how the %s add up or why the NDI only appears on the first two rows of the urbanicity variable. This needs greater clarification

Reply:

Table 1 now reads: (on following page)

		Deprived Neighbourhood				% within Deprived Neighbourh.
Type of patient	Urbanisation level	No (patients)	No (%)	Yes (pat.)	Yes (%)	
Starter Group	1	34662	76.3%	10796	23.7%	86.5%
	2	48673	96.6%	1689	3.4%	13.5%
	3	31107	100.0%	0	0.0%	-
	4	28283	100.0%	0	0.0%	-
	5	11164	100.0%	0	0.0%	-
	total	153889	92.5%	12485	7.5%	100.0%
Continuation Group	1	59714	76.2%	18644	23.8%	85.5%
	2	81406	96.3%	3155	3.7%	14.5%
	3	50853	100.0%	0	0%	-
	4	48511	100.0%	0	0%	-
	5	20754	100.0%	0	0%	-
	total	261237	92.3%	21799	7.7%	100.0%
Total Patients		415126	92.4%	34284	7.6%	

We hope the presentation of the data is clear now. The NDI itself is not available in our data but the dichotomous variable Neighbourhood Deprivation (yes/no) is. All percentages are added up to clarify their calculation. Adapted Table 1 and the legend are added to the original manuscript (original manuscript page 10, line 7 to 27).
The legend now reads: "**The sample is described in absolute numbers for the Starter and the Continuation group, stratified by living in an urbanised area (level 1 to 5), and a dichotomous measure of neighbourhood deprivation. Furthermore, in the last column, tabulation is presented for living in a deprived neighbourhood as a function of level of urbanisation (e.g. in the Starter group, 86.5% of the sample living in deprived neighbourhoods lived in an area with urbanisation level 1)**".

4. P20, line 32-33. Line beginning "Although unlikely to entirely explain the current findings…". Why would this be unlikely? It could be entirely possible. You have no way of deducing the strength of this possibility in the data you have presented. It is important to have acknowledged the possibility of reverse causation, thank you for doing so, but I would drop this line.

Reply: P20, line 13-15 of the original manuscript now reads: "**However, the findings could also be attributed to reverse causation, i.e. patients with worsening pain may move into more urban and deprived neighbourhoods as a consequence of being disabled due to ill health**".
Thus, we dropped the line suggested by reviewer Kirkbride.

5. A statement on ethical approval for this study is required according to the BMJ Open reviewer criteria, but I couldn't see one. This could be easily addressed, I'm sure.

Reply: A statement on ethical approval is added at the end of the article now: "**Data were anonymous, reflecting routine general practice. In the Netherlands, no ethical commission approval is required for analyses using anonymous data acquired in routine practice**" (page 25, line 17 to 19 of the original manuscript). This statement is identical to what has been stated earlier (reply to reviewers' requests concerning manuscript ID BMJopen-2011-000731, and the submission format, which has already been noticed by the editor).

-Well done again on all the changes, the paper reads extremely well now, and will be further improved after consideration of the above points.

Reply: Thank you for the compliment!