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ORIGINAL ARTICLE

Antidepressant prescribing patterns and adverse events following introduction of a National Prescribing Indicator to monitor dosulepin usage in Wales

Katherine Chaplin[1] | Robert C. Bracchi[1] | Kathryn E. Haines[1] | Philip Alexander Routledge[2] | Paul N. Deslandes[1,3]

[1]All Wales Therapeutics and Toxicology Centre, University Hospital Llandough, Llandough, UK

[2]School of Medicine, Cardiff University, Cardiff, UK

[3]Faculty of Life Sciences and Education, University of South Wales, Treforest, UK

Correspondence
Paul N. Deslandes, All Wales Therapeutics and Toxicology Centre, University Hospital Llandough, Llandough, UK.
Email: paul.deslandes@wales.nhs.uk

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Aims: Limiting use of the antidepressant dosulepin has been encouraged due to associated risks of toxicity. In April 2011, the All Wales Medicines Strategy Group introduced a National Prescribing Indicator (NPI) to monitor dosulepin usage. The aim of this study was to investigate antidepressant prescribing patterns, and selected adverse events in patients prescribed dosulepin following introduction of the NPI.

Methods: An e-cohort study was conducted. Adult patients receiving regular dosulepin prescriptions between October 2010 and March 2011 were included. Characteristics of patients who were continued on dosulepin, were switched to an alternative antidepressant or whose dosulepin was discontinued following introduction of the NPI were compared.

Results: In total, 4121 patients were included. Of these, 1947 (47%) continued dosulepin, 1487 (36%) were switched and 692 (17%) discontinued. Of the 692 who discontinued, 92% did not receive a prescription for another antidepressant during the follow-up period. Patients whose dosulepin was discontinued were older and were less commonly coprescribed benzodiazepines. During follow-up, recorded incidence of selected adverse events was low across all groups and no significant difference was observed.

Conclusion: Over half of patients had discontinued dosulepin at the end of the period when the NPI was in place. Further interventions may have been required to have a greater impact on prescribing. This study provides some reassurance that dosulepin discontinuation can be a successful strategy, and that the risk of the adverse events investigated was unlikely to have been greater in those who had dosulepin discontinued than in those in whom dosulepin had been continued.

KEYWORDS
adverse event, antidepressant, dosulepin, prescribing

1 | INTRODUCTION

Depression and anxiety are common mental illnesses associated with long-term morbidity[1,2] and mortality.[3] Drugs used in the treatment of these disorders typically increase synaptic levels of monoamine neurotransmitters such as noradrenaline and serotonin.[4] Serotonin selective reuptake inhibitors (such as sertraline) are typically first line pharmacological treatment options, due to a favourable tolerability

profile. Tricyclic antidepressants (TCAs) such as dosulepin are associated with an increased risk of adverse effects (particularly cardiovascular [CV] toxicity and anticholinergic burden) and are less commonly prescribed in primary care in the UK.[5] Dosulepin is associated with an increased risk of toxicity compared with other antidepressants (with the possible exception of doxepin), particularly when taken in overdose.[6] Discontinuation of dosulepin treatment has been advocated in order to reduce the risk of adverse events.[7] In the UK, both the Medicines and Healthcare products Regulatory Agency and National Institute for Health and Care Excellence made recommendations to limit the use of dosulepin.[8,9] In Wales (UK), the All Wales Medicines Strategy Group (AWMSG) was established in 2002 to provide advice to Welsh Government on aspects of safe and effective prescribing.[10] AWMSG introduced a National Prescribing Indicator (NPI) to monitor dosulepin usage in 2011, and this was subsequently retained for the financial years 2012–2013 and 2013–2014[11] (before being retired from use).

Discontinuation of antidepressant treatment presents significant challenges to both patients and clinicians, including management of emergent withdrawal symptoms and risk of relapse, with limited evidence upon which to base treatment decisions.[12] Despite suggested approaches for managing discontinuation,[13] an optimal method has yet to be determined.[12] Following the introduction of the AWMSG NPI in 2011, dosulepin usage reduced steadily in Wales.[14] Primary care dispensing data obtained from the Comparative Analysis System for Prescribing Audit (NHS Wales Shared Services Partnership) indicated that in April 2011, 6694 prescription items for dosulepin 75-mg tablets were dispensed and submitted for pricing, and, in April 2012, 5028 prescriptions were dispensed and submitted for pricing. This suggested that there may have been approximately 1500 patients whose dosulepin was discontinued in the initial 12-month period following the introduction of the NPI. However, this change in prescribing volume cannot provide information relating to prescribing patterns for individual patients. Following introduction of the NPI, patients previously treated with dosulepin may have remained on treatment, been switched from dosulepin to an alternative antidepressant or may simply have had antidepressant treatment discontinued altogether. The decision to continue, switch or discontinue treatment may have been successful over a subsequent period of time, or patients may have changed to an alternative strategy at a later point.

The aim of this study was to further investigate (at a patient level) prescribing patterns of dosulepin (and any subsequent antidepressant treatment), as well as selected adverse events following the introduction of the AWMSG NPI, using information from a data repository. We sought to identify any unanticipated, significant, adverse consequences that might have occurred due to discontinuation of dosulepin or of switching patients to an alternative antidepressant as a result of the NPI. Demographics of and selected adverse events in 3 distinct groups of patients were studied: (i) those who remained on dosulepin treatment in the period following the introduction of the NPI; (ii) those whose dosulepin treatment was discontinued in the period following the introduction of the NPI; and (iii) those in whom dosulepin was discontinued and who were switched to an alternative antidepressant in the period following the introduction of the NPI.

What is already known about this subject

- Dosulepin is a tricyclic antidepressant, which is associated with risk of toxicity (particularly cardiovascular), including when it is taken in overdose.
- Limiting the use of dosulepin treatment has been advocated by UK national regulatory and advisory bodies in order to reduce the risk of adverse events.
- We have previously shown that dosulepin use in Wales declined steadily following introduction of a National Prescribing Indicator agreed nationally by the All Wales Medicines Strategy Group.

What this study adds

- Following the introduction of the National Prescribing Indicator to promote more rational dosulepin use, 17% of a cohort of 4121 patients in Wales (85% of whom had at least 1 risk factor for cardiovascular adverse effects) had dosulepin discontinued and 36% were switched to another antidepressant.
- Of the 1482 patients who were switched to an alternative antidepressant during the classification period the most common alternatives were mirtazapine (32%), citalopram (32%) and sertraline (11%).
- The recorded incidence of selected adverse events (cardiovascular, self-harm episode or fall) was low in the 3 study groups, and no significant differences in their incidence were observed between the groups who remained on dosulepin, whose dosulepin was discontinued or who were switched to another antidepressant.

2 | METHODS

2.1 | Study design and data sources

This retrospective e-cohort study examined prescribing patterns and selected adverse events in patients prescribed dosulepin in primary care in Wales during and following the period when the dosulepin NPI was introduced in April 2011. Data were obtained from the SAIL databank (www.saildatabank.com).

The SAIL databank is an expanding data repository containing a wide range of anonymized routinely collected person-based data (such as health, education and social care) covering the population of Wales. Clinical and demographic data are provided from several sources, including primary and secondary care records. Records can be linked at an individual level between datasets for the purposes of research. These linkage procedures and approaches of the SAIL databank have been reported previously.[15–17]

Primary care data relating to diagnoses, antidepressant prescribing, comorbidities (binary variables for each of coronary heart disease, stroke/transient ischaemic attack [TIA], diabetes, hypertension, cancer, epilepsy/seizures, osteoarthritis, rheumatoid arthritis, asthma/chronic obstructive airways disease, osteoporosis, liver disease, renal disease) and use of other drugs at baseline (prescribed between October 2010 and March 2011; binary variables for each of antihypertensive drugs, anticoagulants, nonsteroidal anti-inflammatory drugs, anticonvulsants, hypnotics/anxiolytics, antipsychotics, bisphosphonates, oral contraceptives, hormone replacement therapy) were obtained from the Welsh Longitudinal General Practice (WLGP) dataset. Primary care data were available for ~80% of the Welsh population. We extracted demographic characteristics including age at study entry, sex, year of diagnosis of depression, deprivation in fifths (Welsh Index of Multiple Deprivation), ethnic group (categorized as either white/not recorded or nonwhite [Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed]) from the Welsh Demographic Data Service, which contains data on all persons registered with a primary care practice in Wales.

2.2 | Study cohort

The study cohort consisted of people being prescribed dosulepin in Wales. Included individuals were required to be resident in Wales at the onset of the study. Patients were included if they were aged 18 years or over (at April 2011) and if they had received at least 3 consecutive prescriptions (<90-day gap between prescriptions based upon similar studies utilizing information from a primary care research database, for example, Coupland *et al.*[18]) for dosulepin 75-mg tablets in the 6-month period prior to the introduction of the NPI in April 2011 (October 2010 to March 2011). The 75-mg dosulepin formulation was chosen to define study inclusion, as 75 mg is suggested to be the minimum effective dose for the management of depression,[19] and patients were therefore likely to be receiving dosulepin for the ongoing treatment of mental illness. Individuals receiving lower strength formulations of dosulepin during the identification period were not included to avoid those who were already tapering with the aim of discontinuing prior to the introduction of the NPI. Patients were also excluded if they were receiving concurrent treatment with another antidepressant in the 6-month period prior to April 2011. Prior use of amitriptyline (10, 25 and 50 mg) or bupropion was assumed to be for the treatment of pain and smoking cessation, respectively, and allowed. It was estimated that approximately 6500 patients were prescribed dosulepin in Wales in April 2011. Assuming 75% coverage of GP practices in SAIL, data from approximately 4800 patients would be available for inclusion in the study.

2.3 | Study time periods

The study was divided into 3 periods. Period 1 from October 2010 to April 2011 was the identification period, where patients receiving ongoing dosulepin were identified as eligible for inclusion in the study. Period 2 from April 2011 to March 2014 was the classification period, and coincided with implementation of the NPI. Here, we identified whether continuation, discontinuation or switching of patients' dosulepin coincided with the period when the NPI was active. Period 3 was the 2-year follow-up period. For patients whose dosulepin was discontinued or switched, this was the 2-year period following the point of discontinuation of dosulepin. For patients whose dosulepin was continued, this was the 2-year period from April 2014 to April 2016 after the NPI was withdrawn.

2.4 | Grouping of patients

Dosulepin prescriptions issued in general practice between April 2011 and March 2014 were identified and an algorithm used to identify any gaps in dosulepin prescribing (>90-day interval between prescriptions) and any subsequent antidepressant prescriptions during that period. If a gap in dosulepin prescribing was identified, hospital admissions from the Patient Episode Database for Wales were examined. If a hospital admission was found during the 90-day gap then this was not considered a treatment discontinuation. Patients were then subsequently classified into 1 of 3 cohorts:

Group 1. The dosulepin-continuing group, consisting of patients receiving continued prescriptions (no gaps between prescriptions of >90 days) for dosulepin 25- or 75-mg formulations throughout the classification period when the NPI was active (April 2011–March 2014).

Group 2. The discontinuation group, including patients whose dosulepin prescription stopped (defined as a >90-day gap between prescriptions) during the classification period, and who did not receive a subsequent prescription for an alternative antidepressant as identified by specified read code within those 90 days.

Group 3. The switching group, comprising patients whose dosulepin prescription stopped (>90-day gap between prescriptions) during the classification period, and who subsequently initiated an alternative antidepressant within 90 days of last dosulepin prescription.

Patients were followed up for a period of 24 months or until death, whichever was sooner. For the continued cohort, the start of follow-up was defined as 1 April 2014 (the end of the period when the NPI was active). For the discontinued and switching cohorts, the start of follow-up was defined as the date of last dosulepin prescription (before 31 March 2014) plus 30 days (the additional 30 days was based on the assumption that patients would have a remaining 30-day supply following last prescription).

2.5 | Outcomes

All antidepressant prescribing as well as specific adverse events were extracted from WLGP records using the relevant validated read code and/or ICD-10 code.

2.5.1 | Prescribing outcomes

Primary care prescriptions for all antidepressant drugs during the follow-up period of each patient were extracted. Antidepressant drugs were grouped into 3 classes: tricyclic and related antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs) and other antidepressants, including monoamine oxidase inhibitors. A full list of included antidepressants can be found in Table S1.

2.5.2 | Adverse events

Adverse events of interest were all-cause mortality, falls and fractures, CV events (including cardiac arrhythmia, myocardial infarction and stroke/TIA) and self-harm (including attempted suicide). A full list of included read codes is provided in Table S2. The first event occurring during the 2-year follow-up period was identified by relevant read code, and time to event from the start of the follow-up period recorded.

For all-cause mortality, the date and cause of death were taken from the Office for National Statistics deaths register of all deaths relating to Welsh residents, including those who die outside of Wales. Deaths were categorized as unrelated, self-harm, cancer, CV event and CV history.

2.6 | Statistical analysis

Data were analysed using SPSS software (v28). Categorical outcomes were compared using chi-squared tests and for continuous outcomes 1-way ANOVA were conducted. A P value of <.05 was considered statistically significant. *Posthoc* tests were used to identify differences between the 3 cohorts using Bonferroni adjusted P values for categorical outcomes and Tukey *posthoc* tests for continuous outcomes.

2.7 | Governance approval

Approval was gained from the Health Research Authority and Health and Care Research Wales (IRAS project ID 243979). Approval was also granted by the SAIL Information Governance Review Panel (IGRP approval number 0600), an independent body including a range of government, regulatory and professional agencies. The IGRP oversees study approvals in line with permissions already granted for the analysis of anonymous data in the SAIL databank.[15,16]

3 | RESULTS

3.1 | Demographics

At the start of the NPI period (April 2011), 4274 patients were eligible for inclusion. However, 153 died before meeting the classification criteria meaning 4121 patients were included in the study. Of these, 1947 (47%) continued dosulepin throughout the classification period, 692 (17%) had dosulepin discontinued during the classification period and 1482 (36%) were switched to an alternate antidepressant during the classification period (designated as continued, discontinued and switched, respectively). Characteristics of the total included population and the 3 groups outlined above are shown in Table 1. Around 2/3 were female; the mean age was 61 years (standard deviation [SD] 13.1; range 27–92 years). For patients with a depression diagnosis read code recorded, mean time since diagnosis was 15 years (SD 9.9) prior to April 2011.

Overall, the demographic data show that the majority (85%) of patients had at least 1 of the comorbidities of interest. Half (51%) had a history of hypertension, 21% had a history of CV disease and 10% had a history of stroke/TIA. Continuers were significantly more likely to be receiving antipsychotics than the other groups. Patients whose dosulepin was discontinued were significantly older, significantly more likely to be male, significantly less likely to be coprescribed benzodiazepines/z drugs and significantly more likely to have no depression or anxiety diagnoses recorded in their notes than the other groups. Patients who were switched to another antidepressant were significantly younger, significantly more likely to be in the most deprived quintile, significantly less likely to have a history of hypertension, significantly less likely to be prescribed antihypertensive agents and significantly less likely to have no depression or anxiety diagnoses recorded in their notes than the other groups.

3.2 | Prescribing patterns

Of the 4121 patients identified, 3415 (83%) received at least 1 antidepressant prescription during the 2-year follow-up period. Figure 1 shows the first prescription in follow-up by group. The mean number of prescriptions during follow-up was 10 (SD 9.5) in the discontinued group, 28 (SD 21.9) in the continued group and 26 (SD 27.5) in the switched group.

3.3 | Continued group

The first prescription in follow-up was dosulepin for 95% of patients in the continued group. Of those who continued, 1419 (73%) received only dosulepin during follow-up. A total of 70 patients received regular dosulepin prescriptions up to March 2014, but discontinued at the start of the follow-up period (received none or just 1 dosulepin prescription during follow-up). Additionally, 64 continued patients were switched to a different antidepressant at the start of the follow-up

TABLE 1 Characteristics of the study cohort and three groups.

Sociodemographic factors	Continued (*n* = 1947)	Discontinued (*n* = 692)	Switched (*n* = 1482)	Total (*n* = 4121)
Female (%)	69.4	62.9**	69.2	68.2
Age (years), mean (SD)	61.4 (12.3)	63.2 (13.5)	59.2 (13.6)***	61.0 (13.1)
Ethnicity, *n* (%)				
White/not reported	1740 (90)	622 (90)	1342 (91)	3704 (90)
Diagnoses, *n* (%)				
None recorded	366 (19)	166 (24)***	199 (13)	731 (18)
Depression only	773 (40)	283 (41)	650 (44)	1706 (41)
Anxiety only	148 (8)	56 (8)	89 (6)	293 (7)
Both depression and anxiety	660 (34)	187 (27)***	544 (37)	1391 (34)
Time since depression diagnosis (years), mean (SD)	15.4 (9.9)	14.4 (10.5)*	14.5 (9.9)	14.9 (9.9)
Deprivation, *n* (%)				
1 (Most)	335 (17)	114 (17)	300 (20)	749 (18)
2	384 (20)	121 (17)	300 (20)	805 (20)
3	421 (22)	161 (23)	327 (22)	909 (22)
4	388 (20)	145 (21)	249 (17)	782 (19)
5 (Least)	402 (21)	144 (21)	297 (20)	843 (20)
Not reported	17 (0.9)	7 (1.0)	9 (0.6)	33 (0.8)
Medical history, *n* (%)				
At least 1	1650 (85)	598 (86)	1262 (85)	3510 (85)
History of CV event	421 (22)	133 (19)	328 (22)	882 (21)
History of hypertension	1032 (53)	386 (56)	694 (47)***	2112 (51)
History of COPD	371 (19)	124 (18)	290 (20)	785 (19)
History of stroke/TIA	204 (10)	78 (11)	146 (10)	428 (10)
History of diabetes	397 (20)	141 (20)	303 (20)	841 (20)
History of epilepsy/seizures	161 (8)	64 (9)	156 (11)	381 (9)
History of cancer	742 (38)	267 (39)	579 (39)	1588 (39)
Medications,[a] *n* (%)				
At least 1	1667 (86)	581 (84)	1237 (83)	3485 (85)
NSAID	400 (21)	156 (23)	310 (21)	866 (21)
Anticoagulants	53 (3)	21 (3)	39 (3)	113 (3)
HRT[b]	91 (5)	21 (3)	64 (4)	176 (4)
Contraception[b]	5 (0.4)	6 (1.0)	8 (0.5)	19 (0.5)
Anticholinergics	274 (14)	87 (13)	240 (16)*	601 (15)
Anticonvulsants	134 (7)	52 (8)	116 (8)	302 (7)
Antihypertensives	1122 (58)	416 (60)	784 (53)**	2322 (56)
Antipsychotics	261 (13)***	63 (9)	131 (9)	455 (11)
Benzodiazepines/z drugs	582 (30)	138 (20)***	445 (30)	1165 (28)
Opioids	362 (19)	121 (17)	283 (19)	766 (19)
Other	195 (10)	56 (8)	147 (10)	398 (10)

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; TIA, transient ischaemic attack.

[a]Antiparkinson's medication usage not reported due to low numbers.

[b]Percentage of females.

*$P < .05$.

**$P < .01$.

***$P < .001$.

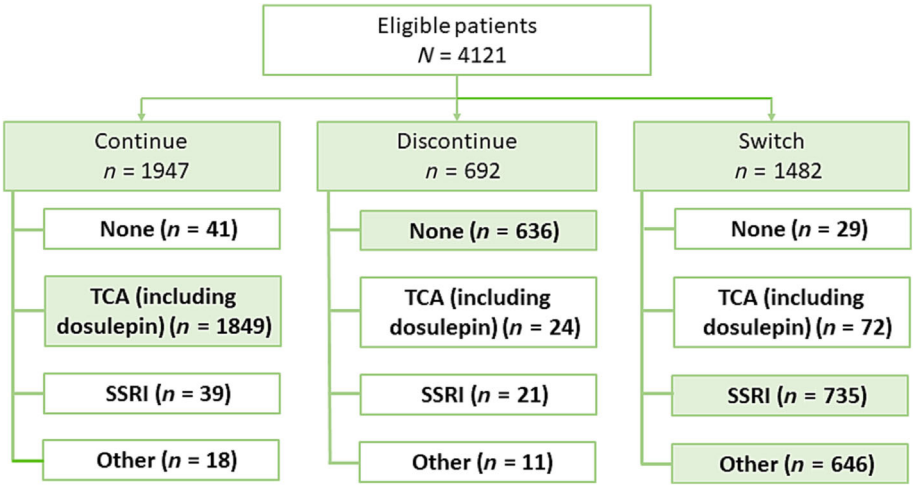

FIGURE 1 First prescription during follow-up. Shading indicates expected prescription based upon classification.

TABLE 2 Antidepressant patients were switched to during the classification period.

	n	%
SSRI	754	51
Citalopram	476	32
Sertraline	166	11
Fluoxetine	103	7
TCA	73	5
Lofepramine	35	2
Clomipramine	15	1
Other	655	44
Mirtazapine (NASSA)	480	32
Trazodone (SARI)	80	5
Duloxetine (SNRI)	68	5
Venlafaxine (SNRI)	25	2

Note: Only the most reported medicines from each group shown.
Abbreviations: NASSA, noradrenergic and specific serotonergic antidepressant; SARI, serotonin receptor antagonists and reuptake inhibitors; SNRI, serotonin–noradrenaline reuptake inhibitor.

TABLE 3 Whether remained on switched-to drug.

Drug	Patients remaining on treatment, *n* (%)	Treatment duration months, mean (standard devation)
Venlafaxine (*n* = 25)	18 (72)	18 (8.2)
Sertraline (*n* = 166)	117 (71)	17 (8.6)
Fluoxetine (*n* = 103)	70 (68)	18 (8.1)
Clomipramine (*n* = 15)	10 (67)	21 (4.7)
Mirtazapine (*n* = 480)	312 (65)	19 (7.8)
Citalopram (*n* = 476)	311 (65)	18 (7.7)
Duloxetine (*n* = 68)	42 (62)	17 (9.6)
Trazodone (*n* = 80)	48 (60)	16 (9.5)
Lofepramine (*n* = 35)	18 (51)	18 (9.0)

period. Of these, 33 (52%) remained on the switched to antidepressant for the duration of the follow-up period.

3.4 | Discontinued group

In the discontinued group, 636 (92%) patients were not prescribed an antidepressant at any point in the follow-up period. However, 3% restarted dosulepin, and 5% were prescribed an alternative antidepressant at some point during the follow-up period.

3.5 | Switched group

Of the 1482 patients who switched to an alternative antidepressant during the classification period the most common alternatives were mirtazapine (32%), citalopram (32%) and sertraline (11%; Table 2). Overall, 95% of patients who switched received either an SSRI or 1 of the other antidepressants. Of those who switched, 973 (67%) received only that antidepressant during the follow-up period. The number of patients remaining on the antidepressant they were switched to (i.e., received no other antidepressant during follow-up) is shown in Table 3. At the end of the follow-up period, 58 (4%) switched patients had restarted dosulepin.

3.6 | First adverse event

Selected adverse events and time to their first occurrence are shown in Table 4. The majority of patients (88%) did not have a recorded

TABLE 4 Adverse events and time to event by group.

Adverse event	Continued ($n = 1947$) *n* (%)	Discontinued ($n = 692$) *n* (%)	Switched ($n = 1482$) *n* (%)	Total ($n = 4121$) *n* (%)
Cardiovascular	85 (4%)	28 (4%)	54 (4%)	167 (4%)
Time to event: days mean (SD)	342 (202)	280 (236)	298 (249)	317 (224)
Self-harm	5 (0.3%)	0	7 (0.5%)	12 (0.3%)
Time to event: days mean (SD)	212 (186)	N/A	125 (112)	161 (147)
Fall	53 (3%)	10 (1%)	31 (2%)	94 (2.3%)
Time to event: days mean (SD)	305 (210)	357 (181)	375 (210)	334 (208)

Abbreviation: SD, standard deviation.

read code for any of the adverse events searched for during the 24-month follow-up period. There were no significant differences in the percentage of patients with any of the adverse events studied between the 3 groups. Mean time to an episode of self-harm was 6 months (161 days, SD 147). For the remaining adverse events, the mean time to event was 12 months (death 336 days, SD 211; CV 317 days, SD 224; fall 334 days, SD 208). No significant differences were found between the groups.

In total, 224 patients (5%) died during study follow-up, 95 (5%) in the continued group, 42 (6%) in the discontinued group and 87 (6%) in the switched group. There were no significant differences in the proportion of patients who died between the groups $\chi^2(2) = 2.26$, P = NS. Time to death, mean (SD) was 361 (197.9) days, 285 (187.2) days and 336 (211.0) days in the continued, discontinued and switched groups, respectively ($F(2, 221) = 1.93$, P = NS). Causes of death identified on the death certificate were cancer ($n = 62$), cardiac event ($n = 6$), cardiac history ($n = 42$), stroke ($n = 12$), suicide ($n = 5$) and other ($n = 96$).

4 | DISCUSSION

Of the 4121 patients prescribed dosulepin and meeting the classification criteria, 47% were continued on dosulepin, 17% had it discontinued and 36% were switched to an alternative antidepressant during the period that the AWMSG NPI was in place. The majority of patients whose dosulepin was discontinued did not receive a prescription for another antidepressant during the follow-up period. The majority of those who were switched to an alternative antidepressant were prescribed either an SSRI or another class of antidepressant (most commonly mirtazapine). The number of read coded selected adverse events noted during the follow-up period was small across all of the groups, with 89% of the cohort having no recorded adverse event of interest.

The mean age of patients included in this study (62 years) was slightly higher than the 45–59 year age group identified as having peak prevalence of depression in a cross-sectional study of a UK sample of the European Health Survey.[20] Furthermore, patients' diagnosis of depression occurred on average 15 years prior to the start of the study, suggesting the cohort may have had relatively longstanding illness overall, or perhaps that treatment had not been reviewed. Antidepressant treatment is recommended for 6–9 months following a first episode and for at least 2 years after subsequent episodes.[19] While ongoing treatment may be justified, dosulepin is associated with adverse CV effects,[21] and anticholinergic effects that may be particularly problematic in older adults.[22] Patients switched from dosulepin to another antidepressant were more commonly coprescribed anticholinergic medicines, and this may in part have been a driver for the change in antidepressant. Patients whose dosulepin was discontinued were older, which may have reflected the perception that the risks of continued dosulepin outweighed the benefits in this group. However, it should be noted that despite statistically significant differences between the groups, ages were numerically similar (mean age of discontinuers = 63 years, SD 13.5, mean age of the whole cohort = 61 years, SD 13.1). Coprescribing of benzodiazepines, and comorbid depression and anxiety were less common in the discontinued group, while those patients remaining on dosulepin were more likely to be coprescribed antipsychotics. Comorbid mental illness is common,[23] and coprescription of other psychotropic medicines was likely to be a marker for this, and for illness that was more difficult to manage. Clinicians may have focused on discontinuing dosulepin in patients where the clinical picture was more straightforward, accounting for these demographic differences between the groups.

Antidepressant discontinuation has been associated with symptom relapse.[24,25] While review of dosulepin treatment to encourage appropriate use was the intended aim of the NPI, an unintended consequence may have been to increase symptom recurrence. Of the 692 patients whose dosulepin was discontinued during the period that the NPI was in place, 92% did not receive another antidepressant during the follow-up period, suggesting that discontinuation was an effective strategy. It should, however, be noted that 36% of the study cohort were switched to an alternative antidepressant. Due to the criteria applied to define switched patients (starting a new antidepressant within 90 days of last dosulepin prescription), it is possible that a proportion of these patients were intended to have their dosulepin discontinued, but perhaps began to experience a recurrence of symptoms or withdrawal effects during these 90 days. An alternate antidepressant may have subsequently been prescribed to manage this. The possibility that switching to an alternate antidepressant might have represented a failed attempt to discontinue dosulepin cannot be

excluded and was a limitation. Psychological intervention has been shown to be an effective strategy to reduce the risk of relapse following antidepressant withdrawal.[26] The proportion of discontinued patients receiving such interventions was not investigated as part of this study, and this was also a limitation.

The drug group most commonly prescribed after switching from dosulepin was SSRIs, with 51% of patients receiving 1 of these drugs as the first medicine after switching. The use of these medicines reflected antidepressant prescribing in the wider population in Wales, where SSRIs were the most widely used group during the period of study. Furthermore, SSRIs have been shown to be the most commonly switched to group in another study of primary care prescribing in the UK.[27] Despite having similar pharmacodynamic properties to dosulepin, other TCAs, venlafaxine and duloxetine were the first switched-to drug in only 11% of patients. These drugs have been associated with higher discontinuation rates than SSRIs.[28] The choice of an SSRI over these alternatives suggested that prescribers perhaps opted for a drug with improved tolerability rather than an equivalent pharmacological action. The 2 most commonly prescribed individual drugs were mirtazapine and citalopram, each accounting for 32% of patients switched. Citalopram was the most commonly prescribed antidepressant in Wales during the study period, accounting for approximately 3 times more items than mirtazapine (https://gov.wales/prescriptions-wales-interactive-dashboard). The common choice of mirtazapine in this cohort (relative to overall antidepressant prescribing) may have been due to greater perceived effectiveness, as suggested by the meta-analysis of Cipriani *et al*.,[28] or perhaps due to its sedating properties, which may have been perceived as similar to dosulepin by prescribers. However, the reasons for subsequent drug choice following dosulepin were not captured in this study and this was a limitation.

Switching antidepressant treatment may be indicated where an initial drug is ineffective or not tolerated.[29] Sixty-seven percent of switched patients remained on the first switched-to antidepressant, suggesting that, in these cases, the new drug was effective and well tolerated and the switch was successful. The mean duration of treatment on the switched-to drug varied with antidepressant, but was approximately 18 months, suggesting further long-term prescription following dosulepin cessation. The remaining 33% of switched patients experienced further switching of their antidepressant, suggesting that the initial choice was either not tolerated or not effective. This potential destabilizing effect on patients' management was a possible disadvantage of the NPI. However, a significant proportion of switched patients were coprescribed drugs such as opioids, antipsychotics, benzodiazepines and anticholinergics, and switching to a safer antidepressant may have helped to reduce the risk of drug interactions and adverse events. The recorded incidence of mortality in our study was higher than the unadjusted rates seen in other studies utilizing primary care databases in the UK.[18,30] This was probably due to the demographics of our cohort, who were on average 20 years older than those in these other studies. Accordingly, a study with an older cohort of patients showed a generally higher incidence of adverse events and mortality associated with TCA use than in our study.[31] However, it was encouraging to note that there were no differences between the 3 cohorts in our study. This suggested that any discontinuation or switching of dosulepin that might have been prompted by the NPI did not appear to result in an increased risk of these adverse events. Although the number of patients experiencing falls was lower in the discontinued and switched groups compared with the continued group (suggesting possible benefit of the NPI), this difference did not reach statistical significance. Furthermore, a greater proportion of the group whose dosulepin was continued were prescribed antipsychotic medicines, and a smaller proportion of those whose dosulepin was discontinued were prescribed benzodiazepines. Both of these factors may have impacted the number of falls observed in each group. The absence of a difference between the groups may also be related to the small number of patients in each group and therefore represent a Type II statistical error. It should be noted that a relatively limited number of adverse events were searched for as part of the study, and the possibility of patients experiencing other effects that were not part of the search strategy cannot be excluded. We did not examine the wider incidence of less serious (but still important) possible adverse events such as constipation and sedation, which may have occurred with greater frequency, but which were more difficult to reliably identify from the data available.

The aim of this study was to investigate further the impact of the AWMSG NPI. While the dataset used provided more information than prescribing data alone, there were a number of limitations. Data collection used read codes from GP systems; therefore, only information that was read coded was captured. As noted above, it was not possible to investigate the reasons for patients to be continued, discontinued or switched nor for the prescribers' choice of antidepressant in the switched group. Stopping antidepressant treatment has been associated with a discontinuation syndrome,[32] and information related to this, and the method of stopping (e.g., gradual tapering of treatment over a given period of time) was not captured in this study. The classification of continuers, discontinuers and switchers was based upon prescriptions issued. It was not possible to determine whether the prescriptions were subsequently dispensed, nor whether the patients took the medicine if it were dispensed. Data corresponding to private prescriptions and prescriptions issued in secondary care were not included in any of our datasets.

Of 4121 patients who were included in the study, 1947 (47%) were still receiving dosulepin at the end of the period in which the NPI was in place. Although further interventions may have been required to have a greater impact on prescribing behaviour, it was encouraging to note that by the end of the NPI period, just over half of patients were no longer prescribed dosulepin. Thirty-six percent of patients had been switched to either an SSRI or other antidepressant and 18% received no prescription for any antidepressant from their GP during follow-up. Following withdrawal of the NPI in April 2014, prescribing of dosulepin in Wales continued to fall. This study provides some reassurance that discontinuation of dosulepin can be a successful strategy and that the risk of the specific adverse events investigated in such individuals would not have been be greater than in those whose dosulepin had been continued.

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AUTHOR CONTRIBUTIONS

Paul N. Deslandes conceived the study. Robert C. Bracchi, Kathryn E. Haines, Philip Alexander Routledge and Paul N. Deslandes contributed to the design of the study. Katherine Chaplin extracted and analysed data. Katherine Chaplin and Paul N. Deslandes were involved with interpretation of data and drafted the manuscript. All authors revised the manuscript and gave approval for publication. All authors take responsibility for the integrity and accuracy of the work.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to declare in relation to this work.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as Supporting Information. Person-level data are not available owing to policies and procedures in place to protect data held in the SAIL databank.

ORCID

Philip Alexander Routledge https://orcid.org/0000-0001-9770-6787

Paul N. Deslandes https://orcid.org/0000-0001-6751-9438

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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