

Association Between Oxybutynin Exposure and Psychiatric and Neurodevelopmental Outcomes in Children with Spina Bifida and Neurogenic Bladder: A Retrospective Cohort Study

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Abstract

Background:

Oxybutynin is widely used to treat neurogenic bladder in children with spina bifida. As oxybutynin readily crosses the blood–brain barrier, concerns remain regarding its potential effects on the central nervous system. However, evidence regarding long-term psychiatric and neurodevelopmental outcomes in children is limited. Therefore, this study evaluated the association between oxybutynin exposure and those outcomes in children with spina bifida and neurogenic bladder.

Methods:

We performed a retrospective cohort study using the TriNetX Research Network. Patients younger than 16 years of age with spina bifida and neurogenic bladder were classified according to oxybutynin exposure within 180 days after diagnosis of neurogenic bladder. The outcomes were newly diagnosed anxiety disorders, mood disorders, neurodevelopmental disorders, and scholastic disorders occurring from day 181 through 15 years after diagnosis. Propensity score matching (1:1) was performed to balance the baseline characteristics. Risk differences (RDs) with 95% confidence intervals (CIs) were calculated in the matched cohorts. Multivariable Cox proportional hazards regression analyses were performed in the entire cohort before matching to identify factors independently associated with each outcome.

Results:

After propensity score matching, 1,342 patients were included in each group. Patients' mean ages were 5.4 ± 4.9 and 5.3 ± 4.9 years in the oxybutynin-exposed and unexposed groups, respectively. Anxiety disorders occurred more frequently in oxybutynin-exposed than unexposed patients (11.6% vs. 7.8%; RD, 3.8%; 95% CI, 1.6–6.0%; $p = 0.001$). Scholastic disorders were also more frequent in the oxybutynin-exposed group than in the unexposed group (7.4% vs. 4.7%; RD, 2.7%; 95% CI, 0.9–4.5%; $p = 0.004$). No significant differences were observed in mood or neurodevelopmental disorders between the groups. In the multivariable Cox regression analyses, oxybutynin exposure was independently associated with anxiety (HR, 1.25; 95% CI, 1.02–1.55) and scholastic disorders (HR, 1.51; 95% CI, 1.18–1.94).

Conclusions:

Among children with spina bifida and neurogenic bladder, oxybutynin exposure was associated with higher incidences of anxiety and scholastic disorders. These findings suggest that monitoring psychiatric and learning-related symptoms may be warranted during long-term oxybutynin therapy.

Background

Neurogenic bladder is a common complication in patients with myelodysplasia, and bladder dysfunction may develop or progress during early childhood because of evolving neurological abnormalities, including those associated with tethered cord syndrome. Without appropriate management, urological complications have been reported in up to 60–80% of affected children within the first few years of life [1]. Anticholinergic medications are considered first-line pharmacotherapy for neurogenic bladder, as they suppress detrusor overactivity and reduce intravesical pressure [2, 3]. In combination with clean intermittent catheterization, anticholinergic therapy protects the upper urinary tract and preserves renal function [4].

Oxybutynin has been used for several decades and remains the most widely used anticholinergic agent. In addition to common adverse effects such as dry mouth, facial flushing, constipation, and blurred vision [3], oxybutynin readily crosses the blood–brain barrier and has a high affinity for M1 muscarinic receptors, raising concerns about potential effects on the central nervous system [5, 6]. In children with spina bifida, drowsiness, hallucinations, and cognitive changes have been reported during oxybutynin treatment [7], while mood changes have also been described in children receiving intravesical oxybutynin for lower urinary tract symptoms [8]. However, pediatric studies evaluating cognitive or behavioral effects have involved small populations or short observation periods, and evidence regarding the long-term neuropsychiatric and neurodevelopmental effects of anticholinergic therapy in children remains limited. Thus, the long-term association between oxybutynin exposure and neurodevelopmental or psychiatric disorders in children with spina bifida remains unclear. We used a large-scale database to evaluate those outcomes in children with spina bifida and neurogenic bladder, allowing for a sufficiently large sample size and extended follow-up.

Methods

Data source

To evaluate the association between oxybutynin exposure and neurodevelopmental or psychiatric disorders in children with spina bifida and neurogenic bladder, we performed a retrospective cohort study using de-identified data obtained from the TriNetX Research Network, a federated global platform integrating electronic health records and insurance claims. At the time of the analysis, the network included data from > 275 million patients treated at 120 healthcare organizations across 19 countries. To safeguard patient confidentiality, the TriNetX platform suppresses any cohort counts ≤ 10 by uniformly displaying them as “10.”

Ethics statements

As all data available for this study were anonymized and aggregated, the requirement for informed consent was waived. The study was determined to be exempt from institutional review board review by

Kagawa University (approval number: 2025 – 170). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, including the 2013 revision adopted in Brazil, and the study methodology and reporting were prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [9]. During the preparation of this work, the authors used ChatGPT (developed by OpenAI) to improve the readability and English grammar of the manuscript. After using this tool, the authors carefully reviewed and edited the content as necessary and take full responsibility for the content of the published article.

Study cohort

The TriNetX database was queried in July 2026, with the study period spanning the previous 20 years. The study population consisted of patients younger than 16 years of age who had diagnoses of both spina bifida and neurogenic bladder, which were ascertained using the relevant International Classification of Diseases, Ninth and Tenth Revision codes (Supplemental Table 1). Patients were classified into two groups according to oxybutynin exposure. The oxybutynin group included patients who received oxybutynin within the first 180 days after the diagnosis of neurogenic bladder. In the control group, patients with any recorded oxybutynin exposure from any time before the diagnosis through the 15-year follow-up period were excluded, thereby restricting this group to patients with no recorded oxybutynin exposure throughout this period. Follow-up for the study outcomes began on day 181 after diagnosis. Patients were excluded if they received medications used for neurogenic bladder that could potentially affect psychiatric or neurodevelopmental outcomes, including other anticholinergic agents, β_3 -adrenoceptor agonists, and tricyclic antidepressants. Additionally, patients with < 1 year of follow-up after the diagnosis of neurogenic bladder were excluded.

Outcomes

Based on previous studies, newly diagnosed anxiety disorders, mood disorders, neurodevelopmental disorders, and scholastic disorders were selected as the outcomes of interest [10, 11]. Patients with any of these diagnoses before or within 180 days after neurogenic bladder diagnosis were excluded. Outcomes were assessed from day 181 up to 15 years after the diagnosis of neurogenic bladder and were identified using the relevant International Classification of Diseases, Tenth Revision code. Detailed definitions and corresponding diagnostic codes are provided in Supplemental Table 1.

Statistical analysis

Propensity score matching (PSM) was performed to improve comparability between the study groups and reduce potential confounding. The variables included in the propensity score model were demographic characteristics (age, sex, race, and ethnicity); congenital and neurological conditions (e.g., presence of hydrocephalus and congenital malformations of the nervous system); neurodevelopmental and psychosocial factors (e.g., broadly defined mental, behavioral, and neurodevelopmental disorders

and abuse or maltreatment); perinatal and neonatal factors (e.g., short gestation and prenatal exposure to harmful substances); family history of epilepsy or other neurological diseases and mental or behavioral disorders; social determinants of health; cerebrospinal fluid shunt procedures; and previous exposure to medications (e.g., antimicrobials, opioid analgesics, anticonvulsants, and sedatives). All the covariates were assessed using data recorded on or before the date of neurogenic bladder diagnosis. Covariates were selected a priori on the basis of previously reported associations with the outcomes of interest and their clinical relevance [11–16]. Detailed definitions of the variables and corresponding codes are presented in Supplemental Table 2. Propensity scores were used to match patients between the two groups at a 1:1 ratio using a nearest-neighbor approach with a caliper of 0.1. The balance of baseline covariates after matching was assessed using absolute standardized mean differences (Std Diffs), with a value < 0.1 considered indicative of adequate balance [17]. Risk differences (RDs) and their 95% confidence intervals (CIs) were calculated to compare outcomes between the matched groups.

To identify factors independently associated with the occurrence of each outcome, multivariable Cox proportional hazards regression analyses were performed in the entire cohort before PSM. Hazard ratios (HRs) with 95% CIs were estimated. Variables included in the models were selected a priori on the basis of previous studies and clinical relevance and included oxybutynin exposure and other potential risk factors [11–16]. Statistical significance was determined using a two-sided p-value < 0.05 or, where applicable, a 95% CI excluding the null value (0 for RD and 1.0 for HR). All the statistical analyses were performed using the analytical tools available within the TriNetX platform.

Results

After PSM, 1,342 patients younger than 16 years of age with diagnoses of both spina bifida and neurogenic bladder between 2006 and 2026 were included in each of the oxybutynin-exposed and unexposed groups (Fig. 1). The sum of excluded cases across categories does not equal the total number of excluded patients because some patients met multiple exclusion criteria. The mean durations of follow-up after the diagnosis of neurogenic bladder were $2,778 \pm 1,510$ and $2,379 \pm 1,499$ days in the oxybutynin-exposed and unexposed groups, respectively.

Table 1 summarizes the baseline characteristics of the oxybutynin-exposed and unexposed groups. Before matching, compared with the unexposed group, the oxybutynin-exposed group was older and had higher proportions of non-Hispanic or Latino patients, those who underwent cerebrospinal fluid shunt procedures, and patients with prior exposure to medications, including antimicrobials and opioid analgesics. After matching, all Std Diff values across the covariates were < 0.1, indicating good balance.

Table 1
Demographic and clinical characteristics of the study patients

Characteristic	All patients ^a			Matched patients		
	Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 4312)	Std Diff	Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 1342)	Std Diff
Age, mean (SD), y	5.4 ± 4.9	4.7 ± 4.8	0.132	5.4 ± 4.9	5.3 ± 4.9	0.016
Sex						
Male	596 (44.4)	2075 (48.1)	0.074	596 (44.4)	574 (42.8)	0.033
Female	746 (55.6)	2235 (51.8)	0.075	746 (55.6)	768 (57.2)	0.033
Unknown gender	0 (0)	10 (0.2)	0.074	0 (0)	0 (0)	NA
Race						
White	818 (61.0)	2468 (57.2)	0.076	818 (61.0)	863 (64.3)	0.069
Black	114 (8.5)	321 (7.4)	0.039	114 (8.5)	105 (7.8)	0.025
Asian	74 (5.5)	192 (4.5)	0.049	74 (5.5)	74 (5.5)	< 0.001
Native Hawaiian or Other Pacific Islander	10 (0.7)	27 (0.6)	0.014	10 (0.7)	10 (0.7)	< 0.001
American Indian or Alaska Native	17 (1.3)	32 (0.7)	0.053	17 (1.3)	16 (1.2)	0.007
Other race	116 (8.6)	344 (8.0)	0.024	116 (8.6)	94 (7.0)	0.061
Unknown race	195 (14.5)	928 (21.5)	0.183	195 (14.5)	184 (13.7)	0.024
Ethnicity						
Non-Hispanic or Latino	795 (59.2)	2180 (50.6)	0.175	795 (59.2)	829 (61.8)	0.052
Hispanic or Latino	332 (24.7)	1085 (25.2)	0.010	332 (24.7)	315 (23.5)	0.030
Unknown ethnicity	215 (16.0)	1047 (24.3)	0.207	215 (16.0)	198 (14.8)	0.035
Std Diff, standardized differences; SD, standard deviation; NA, not applicable.						
^a Actual patient counts ≤ 10 are suppressed to protect privacy and are reported as “10.”						

Characteristic	All patients ^a			Matched patients		
	Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 4312)	Std Diff	Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 1342)	Std Diff
Congenital and neurological conditions						
Spina bifida	985 (73.4)	3121 (72.4)	0.023	985 (73.4)	1023 (76.2)	0.065
Spina bifida occulta	54 (4.0)	238 (5.5)	0.070	54 (4.0)	52 (3.9)	0.008
Hydrocephalus	258 (19.2)	656 (15.2)	0.106	258 (19.2)	230 (17.1)	0.054
Congenital malformations of the nervous system	1077 (80.3)	3492 (81.0)	0.018	1077 (80.3)	1090 (81.2)	0.025
Diseases of the nervous system	576 (42.9)	1754 (40.7)	0.046	576 (42.9)	553 (41.2)	0.035
Chromosomal abnormalities	27 (2.0)	83 (1.9)	0.006	27 (2.0)	23 (1.7)	0.022
Neurodevelopmental and psychosocial factors						
Mental, behavioral, and neurodevelopmental disorders	103 (7.7)	378 (8.8)	0.040	103 (7.7)	107 (8.0)	0.011
Adult and child abuse, neglect, and other maltreatment	10 (0.7)	11 (0.3)	0.070	10 (0.7)	10 (0.7)	< 0.001
Perinatal and neonatal factors						
Disorders of newborn related to short gestation and low birth weight	56 (4.2)	179 (4.2)	0.001	56 (4.2)	57 (4.2)	0.004
Newborn affected by noxious substances transmitted via the placenta or breast milk	10 (0.7)	12 (0.3)	0.065	10 (0.7)	10 (0.7)	< 0.001
Std Diff, standardized differences; SD, standard deviation; NA, not applicable.						
^a Actual patient counts ≤ 10 are suppressed to protect privacy and are reported as “10.”						

Characteristic	All patients ^a		Std Diff	Matched patients		
	Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 4312)		Oxybutynin group (n = 1342)	Non-oxybutynin group (n = 1342)	Std Diff
Newborn affected by other complications of labor and delivery	10 (0.7)	20 (0.5)	0.036	10 (0.7)	10 (0.7)	< 0.001
Family history						
Family history of epilepsy and other diseases of the nervous system	10 (0.7)	12 (0.3)	0.065	10 (0.7)	10 (0.7)	< 0.001
Family history of mental and behavioral disorders	10 (0.7)	18 (0.4)	0.043	10 (0.7)	10 (0.7)	< 0.001
Social determinants of health						
Social determinants of health	10 (0.7)	16 (0.4)	0.050	10 (0.7)	10 (0.7)	< 0.001
Procedures						
Cerebrospinal fluid shunt procedures	81 (6.0)	146 (3.4)	0.125	81 (6.0)	68 (5.1)	0.042
Medications						
Antimicrobials	688 (51.3)	1,483 (34.4)	0.346	688 (51.3)	680 (50.7)	0.012
Glucocorticoids	261 (19.4)	735 (17.0)	0.062	261 (19.4)	236 (17.6)	0.048
Thyroid modifiers	13 (1.0)	26 (0.6)	0.041	13 (1.0)	14 (1.0)	0.007
Opioid analgesics	393 (29.3)	989 (22.9)	0.145	393 (29.3)	377 (28.1)	0.026
Anticonvulsants	77 (5.7)	169 (3.9)	0.085	77 (5.7)	65 (4.8)	0.040
Barbituric acid sedatives	43 (3.2)	90 (2.1)	0.070	43 (3.2)	32 (2.4)	0.050
Benzodiazepine sedatives	294 (21.9)	710 (16.5)	0.139	294 (21.9)	277 (20.6)	0.031
Std Diff, standardized differences; SD, standard deviation; NA, not applicable.						
^a Actual patient counts ≤ 10 are suppressed to protect privacy and are reported as “10.”						

Table 2
Comparison of clinical outcomes between the oxybutynin and non-oxybutynin groups

Outcome	Oxybutynin group (n = 1,342)	Non-oxybutynin group (n = 1,342)	Risk difference (95% confidence interval)	p-value
Anxiety disorders	156 (11.6)	105 (7.8)	0.038 (0.016, 0.060)	0.001
Mood disorders	62 (4.6)	59 (4.4)	0.002 (-0.013, 0.018)	0.78
Neurodevelopmental disorders	116 (8.6)	116 (8.6)	0.0 (-0.021, 0.021)	1.0
Scholastic disorders	99 (7.4)	63 (4.7)	0.027 (0.009, 0.045)	0.004

Table 2 summarizes the clinical outcomes after PSM. Anxiety disorders occurred in 156 (11.6%) oxybutynin-exposed patients and 105 (7.8%) unexposed patients. Similarly, scholastic disorders occurred in 99 (7.4%) versus 63 (4.7%) patients. By contrast, no significant differences were observed in mood disorders or neurodevelopmental disorders between the groups.

Table 3
Factors associated with anxiety disorders

Covariate	Hazard ratio	95% CI	p-value
Male	0.63	(0.52, 0.76)	< 0.001
Age	1.05	(1.03, 1.07)	< 0.001
White	1.69	(1.37, 2.08)	< 0.001
Non-Hispanic or Latino	1.25	(1.03, 1.53)	0.025
Oxybutynin group versus non-oxybutynin group	1.25	(1.02, 1.55)	0.034
Pre-index oxybutynin use	0.71	(0.48, 1.05)	0.085
Hydrocephalus	0.86	(0.65, 1.15)	0.317
Family history of mental and behavioral disorders	NA	NA	NA
Disorders of newborn related to short gestation and low birth weight	0.75	(0.38, 1.46)	0.396
Antimicrobials	1.63	(1.34, 1.98)	< 0.001

CI, confidence interval; NA, not applicable.

Factors independently associated with anxiety disorders in the multivariable Cox proportional hazards regression analysis included older age, White race, non-Hispanic or Latino ethnicity, oxybutynin exposure, and antimicrobial exposure, whereas male sex was associated with a lower risk (Table 3).

Table 4
Factors associated with scholastic disorders

Covariate	Hazard ratio	95% CI	p-value
Male	1.26	(1.00, 1.60)	0.053
Age	0.99	(0.97, 1.02)	0.53
White	1.01	(0.79, 1.30)	0.92
Non-Hispanic or Latino	1.52	(1.18, 1.97)	0.001
Oxybutynin group vs. non-oxybutynin group	1.51	(1.18, 1.94)	0.001
Antimicrobials	1.77	(1.40, 2.26)	< 0.001

CI, confidence interval.

Factors independently associated with scholastic disorders in the multivariable Cox proportional hazards regression analysis included non-Hispanic or Latino ethnicity, oxybutynin exposure, and antimicrobial exposure (Table 4).

Discussion

This study, which analyzed a large cohort of 2,684 children with spina bifida and neurogenic bladder after PSM, yielded two important findings. First, the incidences of both anxiety and scholastic disorders were significantly higher in children exposed to oxybutynin than in those without oxybutynin exposure. Second, results of the multivariable Cox regression analyses showed that oxybutynin exposure was independently associated with both anxiety and scholastic disorders. These findings suggest that oxybutynin exposure may be associated with specific psychiatric and neurodevelopmental outcomes in children with spina bifida and neurogenic bladder.

Previous studies on the neurobehavioral effects of anticholinergic therapy in children have yielded inconsistent findings. Veenboer et al. evaluated 32 children with spinal dysraphism, including 16 children with long-term antimuscarinic exposure, with a median treatment duration of 8.3 years [16]. Behavioral and emotional problems were assessed using the Child Behavior Checklist, and no significant differences in the total problem scores or any of its subdomains were observed between children with and without long-term antimuscarinic use. Although these findings differ from the associations observed here, the small sample size may have limited the ability to detect differences in individual behavioral outcomes. By contrast, Wong et al. evaluated children receiving oxybutynin for non-neurogenic lower urinary tract symptoms and reported mood changes in 15 of 146 patients (10.3%) and hallucinations in 2 patients (1.4%) [8]. Lee et al. retrospectively evaluated 121 children with neurogenic bladder associated with spinal dysraphism who received oxybutynin for a mean treatment duration of 576 days (range, 30–3,330 days) and reported drowsiness in two patients (1.7%) [18]. Differences in study populations, outcome definitions, treatment duration, and methods of outcome assessment may partly explain the

variation in findings across the studies. Nevertheless, despite differences in the types and frequencies of reported symptoms, the results of previous studies on mood changes, hallucinations, and drowsiness suggest that oxybutynin can exert effects on the central nervous system in children.

The route of oxybutynin administration may also influence its effects on the systemic and central nervous system. Intravesical administration has been associated with fewer systemic adverse effects and better tolerability than oral administration in children with neurogenic bladder [7, 19]. This difference may be partly explained by reduced first-pass metabolism after intravesical administration, resulting in lower exposure to the active metabolite N-desethyl-oxybutynin [20]. In a pharmacokinetic study of children with neurogenic bladder, Buyse et al. demonstrated markedly lower N-desethyl-oxybutynin-to-oxybutynin ratios following intravesical administration compared with oral administration [20]. Nevertheless, intravesical administration does not eliminate adverse effects on the central nervous system. Ferrara et al. reported drowsiness, hallucinations, and cognitive changes among children receiving intravesical oxybutynin [7]. Given the potential differences in pharmacokinetics and effects on the central nervous system between these routes of administration, this limitation may have influenced the observed associations.

The observed associations may be biologically plausible given the pharmacological properties of oxybutynin. Oxybutynin is a lipophilic tertiary amine that readily crosses the blood–brain barrier and binds to muscarinic receptors in the brain [5]. Muscarinic receptors in the central nervous system are involved in cognitive processes, including learning and memory, providing a potential biological mechanism for the cognitive effects of oxybutynin [5]. Importantly, central nervous system penetration differs among anticholinergic agents. For example, oxybutynin shows extensive central nervous system penetration, whereas agents such as darifenacin and trospium exhibit substantially lower penetration [21]. Therefore, the present findings should not necessarily be generalized to all anticholinergic medications used for neurogenic bladder. These pharmacological differences suggest that the choice of anticholinergic agent may be relevant when long-term therapy is required, particularly in children.

This study had some limitations. Owing to its retrospective observational design, causal relationships cannot be established, and residual confounding may remain despite PSM. In particular, detailed clinical information reflecting the severity of neurogenic bladder and spina bifida, including urodynamic findings, lesion level, and neurological function, was not available. Additionally, the medication records do not necessarily reflect actual medication use, and detailed information regarding drug adherence, dosage, treatment duration, and cumulative oxybutynin exposure could not be fully assessed. Further, the route of oxybutynin administration could not be reliably determined from the database and was, therefore, not accounted for in the analysis. Anxiety and scholastic disorders were also identified using diagnostic codes rather than standardized psychiatric, neuropsychological, or educational assessments, potentially resulting in outcome misclassification. Finally, compared with their counterparts, children receiving oxybutynin may have had more frequent contact with healthcare providers because of ongoing management of neurogenic bladder, potentially increasing the likelihood of detecting and diagnosing psychiatric or neurodevelopmental conditions and introducing surveillance bias.

Despite these limitations, this study evaluated long-term psychiatric and neurodevelopmental outcomes in a large cohort of children with spina bifida and neurogenic bladder. Given that oxybutynin remains widely used and may be initiated as early as infancy in children with spina bifida, its potential effects on the central nervous system are particularly important because treatment may occur during critical periods of cognitive, emotional, and educational development.

Conclusions

Among children with spina bifida and neurogenic bladder, oxybutynin exposure was associated with higher incidences of anxiety and scholastic disorders. Our findings highlight the importance of monitoring psychiatric and learning-related symptoms during long-term oxybutynin therapy.

Abbreviations

PSM, propensity score matching; Std Diff, standardized mean difference; RD, risk difference; CI, confidence interval; HR, hazard ratio

Declarations

Ethics approval and consent to participate

As all data available for this study were anonymized and aggregated, the requirement for informed consent was waived. The study was determined to be exempt from institutional review board review by Kagawa University (approval number: 2025 – 170).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Takayuki Fujii: Conceptualization; investigation; funding acquisition; methodology; visualization; validation; writing – original draft; formal analysis. Yui Noguchi: Supervision; writing – review. Nanami Harada: Supervision; writing – review. Hiroto Katami: Supervision; writing – review. Aya Tanaka: Conceptualization; supervision; writing – review.

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Data Availability

The data that support the findings of this study are available from TriNetX, LLC. Restrictions apply to the availability of these data, which were used under license for this study and are therefore not publicly available. The aggregated data generated from the analyses are available from the corresponding author upon reasonable request.

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Figures

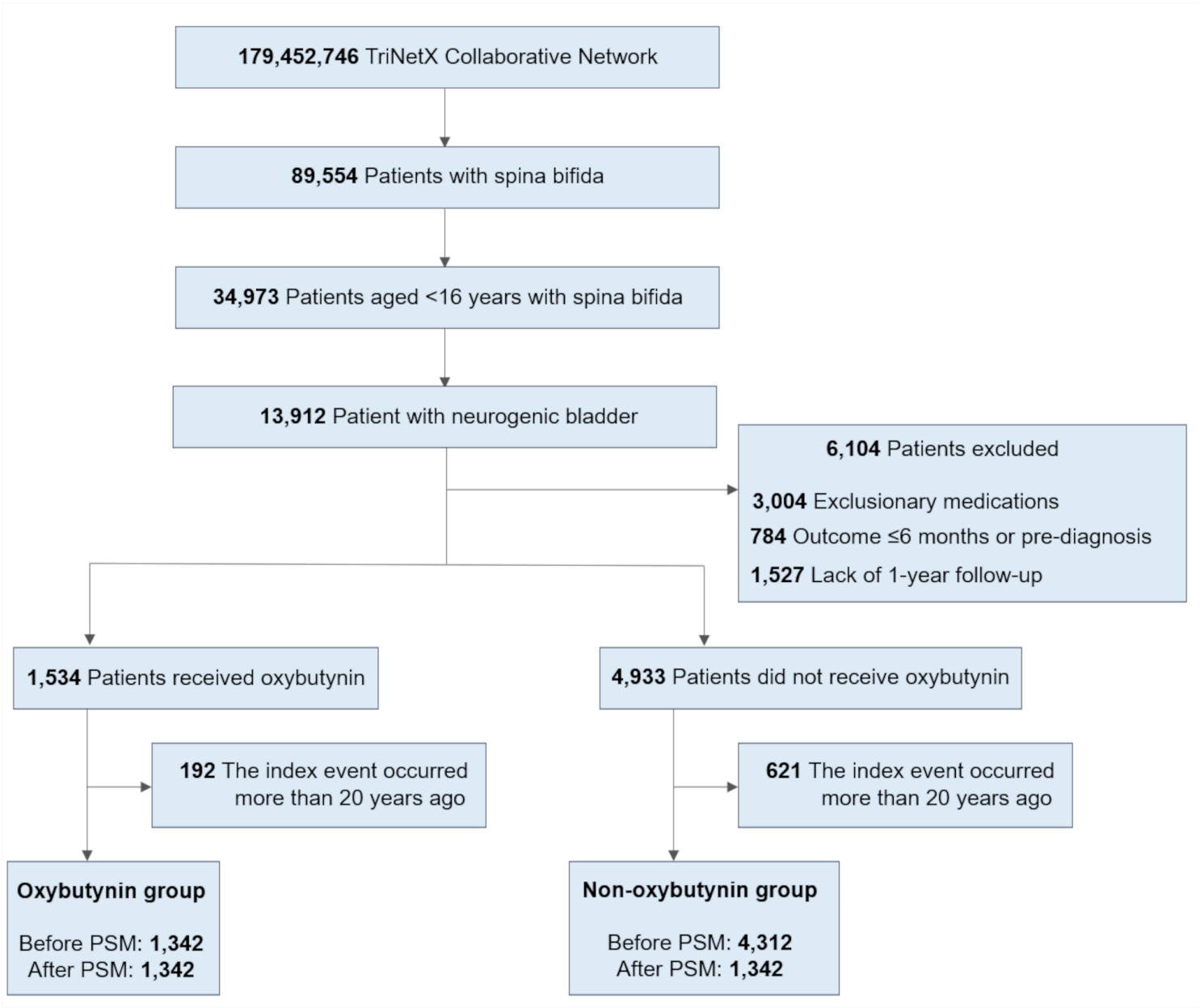


Figure 1

Study flow diagram

The sum of excluded cases across categories does not equal the total number of excluded patients because some patients met multiple exclusion criteria. Abbreviations: PSM, propensity score matching

Supplementary Files

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- [SupplementalTable1.CodesUsedtoIdentifyStudyCohort.docx](#)

- [SupplementalTable2.CodesUsedtoIdentifyStudyCovariates.docx](#)