

Opioid-containing antitussives in Switzerland: a descriptive cross-sectional time-series analysis of pharmacy sales 2013–2022

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Summary

BACKGROUND: Opioid-containing antitussives are used to symptomatically treat a dry, irritative cough but bring a risk of misuse as recreational drugs. Since the update of the Swiss Therapeutic Products Act in 2019, opioid-containing antitussives are regulated more strictly, being available only on prescription and no longer over the counter.

AIM: This study aimed to describe the sales trends of opioid-containing antitussives in Switzerland between 2011 and 2022 to assess the impact of the regulation change.

METHODS: We descriptively analysed cross-sectional data of opioid sales from wholesalers to pharmacies and self-dispensing physicians as an indicator of community use.

MAIN FINDINGS: An estimated 369 million standard units of opioid-containing antitussives were sold over the whole observation period, of which 59% contained dextromethorphan as the active ingredient. Sales decreased slowly between 2011 and 2019, then dropped substantially in 2020 (–30.4% compared to previous year) and 2021 (–15.2%), then partially recovered in 2022. The sales of codeine-containing antitussives did not recover until the end of the study period (quarter 3 of 2022) and remained 37.3% lower than before the rescheduling (quarter 4 of 2018).

DISCUSSION: It is likely that repeated media attention on cases of misuse of opioid-containing antitussives led to more cautious dispensing in Switzerland leading up to the revision of the Therapeutic Products Act in 2019. The substantial decrease in sales in 2020 and 2021 was likely related to the COVID-19 pandemic rather than the rescheduling of opioid-containing antitussives. Longer data collection will be needed to assess the impact of the regulation change post-pandemic.

Introduction

Acute respiratory tract infections, including acute coughs, are among the most frequent conditions pharmacists encounter in their daily practice [1]. Medications containing codeine, codeine derivatives or dextromethorphan, hereinafter “opioid-containing antitussives”, are used to symp-

tomatically treat a dry, irritative cough – despite a relative lack of evidence of their efficacy [2].

In the late 2000s, concerns started emerging in the USA about the misuse of opioid-containing antitussives as recreational drugs by teenagers, a trend which subsequently spread to Europe, including Switzerland [3, 4]. A survey conducted in 2018 among 1180 Swiss adolescents found that one in six 20-year-olds had used codeine cough syrup recreationally [5], a number which might even be an underestimate, as found in later hair analyses of the survey participants [6]. Risks of codeine misuse include respiratory depression and dependence. Dextromethorphan overdose can lead to seizures and coma [7, 8].

In 2019, the Swiss Therapeutic Products Act was updated and included a revision of the Swiss drug dispensing categories. All medications had previously been classified into categories A–E based on the required dispensing authority, with category A being the most restrictive (single dispensing requiring a medical prescription) and category E being the least restrictive (over-the-counter [OTC] without medical advice). Category C (medications dispensed by pharmacists) was abolished in the new classification, and all medications in this category underwent a risk-based reclassification to either category D (over-the-counter dispensing with specialist advice) or category B (dispensing requiring a medical prescription). More specifically, drugs reclassified from category C to category B received a special status, in that these can be dispensed by pharmacists after a documented consultation. Opioid-containing antitussives, which were previously in category C, fell into this so-called B+ dispensing category due to their risk of misuse [9, 10].

Despite regular media attention and this significant regulation change, an investigation of the utilisation of opioid-containing antitussives in Switzerland has not been conducted to date. This study aims to close this gap by describing the sales trends of opioid-containing antitussives in Switzerland between 2011 and 2022.

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Methods

Study design and data sources

We conducted a descriptive interrupted time-series analysis using repeated cross-sectional data on drug sales in Switzerland. Data was derived from the IQVIA MIDAS[®] pharmaceutical sales database for the period between quarter 1 (Q1) 2013 and Q3 2022. IQVIA MIDAS[®] is a dataset that tracks sales volumes and values across 94 countries and over 1.6 million drug products, reflecting estimates of real-world activity. This includes hospital and retail pharmacy channels but does not include information about individual facilities. For our analysis, drug sales within the retail channel, which includes pharmacies and self-dispensing physicians (i.e. physicians who own their own dispensary), were used as an indicator of community use. This data included the year, calendar quarter (Q), Anatomical Therapeutic Chemical (ATC) code of the medication and the total number of standardised units sold. A standardised drug unit is defined as a single tablet/capsule, patch, vial or 5 ml of oral liquid. The data exhibited no missing values. To validate the data, we performed a cross-check of the included products and the products approved and distributed on the Swiss market and ensured that sales numbers were within a reasonable range.

We included all sales and variables for the following ATC codes in the category *R05 cough and cold preparations*: *R05DA04 codeine*, *R05DA09 dextromethorphan*, *R05FA02 opium derivatives and expectorants*. Products under the ATC code *R05FA02* containing the non-narcotic opioid noscapine were excluded from our analysis as their regulatory status did not change. The ATC code *R05DA20 opium alkaloids and derivatives* was not included as it included only one product and would thus reveal information outside the scope of the licensing agreement with IQVIA MIDAS. While dextromethorphan-containing antitussives do not primarily act at opioid receptors, we included products under *R05DA09 dextromethorphan* in our analysis as they pose the same concerns regarding misuse as opioid-containing antitussives and were thus treated equally to codeine and codeine derivatives and combination products during the regulation change of 2019 [7, 11]. Combination cold medicines containing dextromethorphan are classified under the ATC code *N02BE51 Paracetamol, combinations excl. psycholeptics* and were outside the scope of the regulation change and of our analysis. In a post hoc analysis, the ATC code *R05DB13 butamirate* was added to the analysis to serve as a control, as butamirate-containing products were not affected by the regulation change.

Statistical analysis

We analysed quarterly sales data from Q1 2013 to Q3 2022. The quarterly sales were standardised to the Swiss population (rate per 100,000). Swiss population statistics for the years 2013 to 2022 were obtained from the Swiss Federal Statistical Office [12].

We conducted a descriptive time-series analysis to plot and visualise the development of quarterly sales of antitussives in Switzerland between Q1 2013 and Q3 2022. To assess time trends, the time series was decomposed with Seasonal and Trend decomposition using LOESS, resulting in a

trend component which excludes the seasonal fluctuation and random noise from the data.

To assess fluctuations in sales, annual sales rates were calculated as the sum of the sales rates across all four quarters in the year for years with complete data (2013–2021). The percent change in sales rate was determined by comparing it to the previous year.

All analyses were conducted for the cumulative sales of all ATC codes and stratified by ATC code. To visualise the timing of the reclassification, we defined a range for each ATC class given that the roll-out of the reclassification occurred throughout 2019 and the date of upregulation for each antitussive medication varied (see appendix table S1). Additionally, we included the start and end of the COVID-19 pandemic in Switzerland as previous studies have shown the impact of COVID-19 on medication utilisation [13]. The COVID-19 pandemic start and end dates were determined as 28 February 2020 and 31 March 2022, respectively, in accordance with the proclamation and end of the “special situation” according to Article 6 of the Swiss Epidemics Act [14] as communicated in press releases by the Swiss Federal Council [15, 16].

No protocol has been preregistered for this descriptive study.

Statistical analyses were performed using R statistical software (version 4.0.4) [17]: data was plotted using *ggplot2* [18] and the Seasonal and Trend decomposition using LOESS was performed with *forecast* [19].

Ethics approval

This study did not use any individual participant or patient data, and therefore is exempt from research ethics review. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [20].

Results

Between Q1 2013 and Q3 2022, an estimated 324 million standard units of opioid-containing antitussives were sold. The majority of sales were for preparations containing dextromethorphan (an estimated 191 million standard units, 59%), followed by codeine preparations (27%), and opioid and expectorant combination products (14%) (see table 1).

The quarterly sales rate trends are plotted in figure 1 for the overall and individual ATC classes (appendix table S3 provides the corresponding rates). While there was variation in the sales rate, the decomposed trend line shows a

Table 1:

Sales volumes and shares of opioid-containing antitussives over the whole study period, Q1 2013 – Q3 2022. Sales are in standard units. Author analysis based on IQVIA MIDAS[®] quarterly volume sales data for Q1 2013 – Q3 2022, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

Substance	Total estimated sales Q4 2011 – Q3 2022 in million standard units	Percent of all antitussive sales
All	324	100%
Codeine	87	27%
Dextromethorphan	191	59%
Opioids and expectorants	46	14%

sharp decrease in all sales (figure 1) at the end of 2019; however, the sales rate had nearly returned to baseline by the end of 2021. The sales of butamirate-containing antitussives showed a very similar trend as opioid-containing antitussives between 2020 and 2022; however, butamirate-containing antitussive sales increased further after 2022. The sales rates, decomposed trend and the corresponding graph can be found in appendix table S4 and appendix figure S2.

Table 2 provides the annual sales rate per 100,000 for years with complete data (2013–2021) and the percent change vs the previous year. Overall, antitussive sales fluctuated between 2012 and 2019; however, sales decreased substantially in 2020. In 2020, 30.5% less opioid-containing anti-

tussives were sold than in 2019. A similar decline in 2020 was seen for all individual ATC codes with dextromethorphan sales decreasing the least (–27.8%) and opioid and expectorant sales decreasing the most (–39.9%) compared to the previous year.

Discussion

While the sales of opioid-containing antitussive medications were slowly decreasing prior to the reclassification that occurred throughout 2019, the sales rates decreased substantially in Q4 of 2019. Although we observed a decrease prior to the start of the COVID-19 pandemic in

Figure 1: Antitussive sales trends per substance class. The sales are units sold per 100,000 population. The green line shows the raw data, while the black line shows the trend component remaining after time-series decomposition with LOESS. Graphs including the seasonal and remainder components and the underlying data can be found in appendix figure S1. The period in which the products in the respective category were upregulated is marked in grey; the period of the COVID-19 pandemic is marked in orange. Author analysis based on IQVIA MIDAS® quarterly volume sales data for Q1 2013 – Q3 2022, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

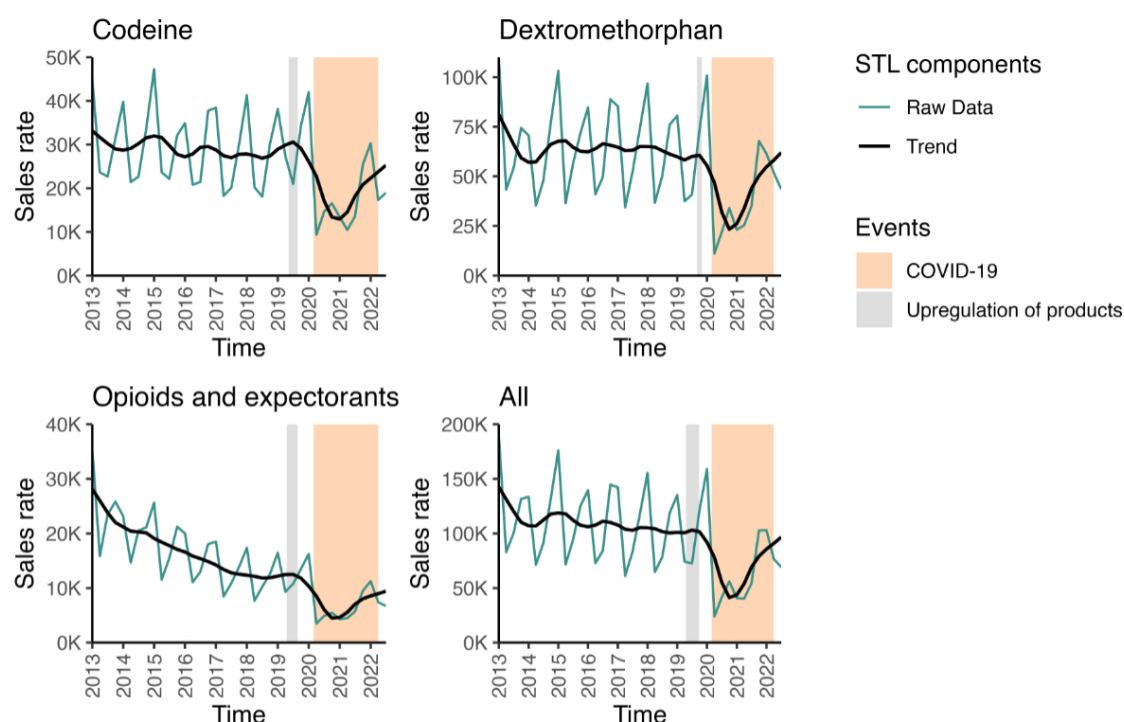


Table 2:

Estimated cumulative annual sales rates (units sold per 100,000 population; complete years only) and change in comparison to the immediately preceding year. Crude estimated sales rates and changes are in appendix table S2. Author analysis based on IQVIA MIDAS® quarterly volume sales data for Q1 2013 – Q3 2022, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

	All		Codeine		Dextromethorphan		Opioids and expectorants	
Period	Estimated sales rate	Change [%]	Estimated sales rate	Change [%]	Estimated sales rate	Change [%]	Estimated sales rate	Change [%]
2013	504,614	–	122,932	–	281,059	–	100,623	–
2014	427,924	–15.2%	117,531	–4.4%	230,929	–17.8%	79,463	–21.0%
2015	467,181	9.2%	125,218	6.5%	268,059	16.1%	73,904	–7.0%
2016	441,222	–5.6%	114,920	–8.2%	264,210	–1.4%	62,092	–16.0%
2017	405,139	–8.2%	106,904	–7.0%	246,559	–6.7%	51,676	–16.8%
2018	417,533	3.1%	109,848	2.8%	259,875	5.4%	47,810	–7.5%
2019*	403,176	–3.4%	120,784	10.0%	232,376	–10.6%	50,017	4.6%
2020**	280,402	–30.5%	82,529	–31.7%	167,808	–27.8%	30,065	–39.9%
2021**	238,099	–15.1%	62,832	–23.9%	151,294	–9.8%	23,973	–20.3%

* 2019: period of product upregulation

** 2020 and 2021: time of the COVID-19 pandemic in Switzerland

Switzerland, the substantial decrease in sales in 2020 is likely largely due to the effects of the pandemic rather than the reclassification.

Having only been completed in late 2019, the effect of the reclassification of opioid-containing antitussives on the 2019 sales rates is difficult to discern given the proximity to the start of the COVID-19 pandemic. However, we do note that the sales rate decreased by 3.4% in 2019 compared to 2018, and the quarterly data shows that most opioid-containing antitussives have not returned to 2018 levels. This may indicate that the reclassification has slightly curbed sales, particularly for codeine-containing antitussives.

The sales of antitussives containing dextromethorphan, or opioids combined with expectorants appear to be gradually increasing post-pandemic; however codeine-containing antitussives only saw a partial recovery of the sales rate. At the end of the study period in Q3 2022, sales were 37.2% lower than in Q4 of 2018. In 2015, the European Medicines Agency issued a contraindication for the use of codeine-containing antitussives in children younger than 12 years, as well as in patients with known ultrarapid metaboliser status in the CYP2D6 enzyme [21]. This contraindication was adopted in Switzerland in 2017 [22]. Therefore, it is also possible that combination products containing additional active ingredients for the symptomatic treatment of acute respiratory infections (e.g. butamirate) are increasingly favoured over codeine mono-preparations with the aim of improving treatment efficacy, given that the antitussive properties of codeine do not seem to outperform placebo [23]. However, concerns and additional restrictions placed on codeine use have little impact on the sales of all opioid-containing antitussives cumulatively as dextromethorphan remains the most popularly used opioid-containing antitussive in Switzerland. While dextromethorphan does not act at opioid receptors, its misuse potential is similar to that of codeine [24] and dextromethorphan monopreparations have thus undergone the same regulatory changes as codeine-containing antitussives [11]. The media coverage on antitussive misuse and the ensuing regulation change in Switzerland was, however, mainly focused on codeine-containing antitussives [25–28]. This might suggest that the revision of the Therapeutic Products Act had a larger impact on codeine-containing than on dextromethorphan-containing antitussives. On the other hand, calls to the Swiss poisons information centre Tox Info Suisse for dextromethorphan poisonings have been decreasing since 2017 [29]. As data after 2020 is not available from this source, it remains unclear how the poisoning trends have been impacted by or evolved since the COVID-19 pandemic.

However, as identified, the estimation of the effect of the Therapeutic Products Act revision on the sales of opioid-containing antitussives is complicated by the start of the COVID-19 pandemic in February 2020, which affected drug sales through various mechanisms [13]. Firstly, people who contracted COVID-19 were obliged to isolate at home and were thus unlikely to seek treatment at a pharmacy. Therefore, as opioid-containing antitussives under the new Therapeutic Products Act can only be dispensed to the patient personally, non-opioid antitussives (from dispensing category D) would have been favoured when sold to

caregivers. Secondly, due to the protective measures taken during the pandemic, other respiratory tract infections such as seasonal influenza had a very low incidence in the 2020/2021 season [30], likely also minimising the necessity for treating cough from respiratory tract infections other than COVID-19 and decreasing sales of opioid-containing antitussives. While the pandemic broadly affected supply chains for drugs which led to shortages, the effect on opioid-containing antitussives specifically was relatively small [31]. Lastly, a study by Gordon and colleagues published in March 2020 found that dextromethorphan increased the titres of SARS-CoV-2 *in vitro* [32]. The authors, and subsequently several news outlets, called for caution in the use of dextromethorphan-containing antitussives for the symptomatic treatment of COVID-19 [33–35]. To what extent this affected the sales of dextromethorphan-containing antitussives is unclear; however, in our study dextromethorphan-containing antitussives saw a smaller decrease (–27.8%) in 2020 compared to 2019 than codeine-containing antitussives (–31.7%) and opioid and expectorants (–39.9%). To better distinguish the effects of COVID-19 from those of the revision, we additionally analysed the sales trends of butamirate-containing antitussives which were not reclassified and thus unaffected by the regulation. To date, butamirate-containing antitussives are still available over-the-counter [36]. We found that butamirate-containing antitussive sales trends developed very similarly to the sales trends of opioid-containing antitussives during the COVID-19 pandemic in that there was a sharp drop during 2020 followed by an increase in 2021. However, while the sales of opioid-containing antitussives merely returned to pre-upregulation levels (Q4 2018 vs Q3 2022: –3.8%), the sales of butamirate-containing antitussives were 40.6% higher at the end of our observation period than in Q4 of 2018. On the one hand, this suggests that the drop in sales of opioid-containing antitussives in 2020 was indeed mainly driven by the circumstances of the pandemic; on the other hand, the following rise in butamirate sales might be a consequence of fewer sales of codeine-containing antitussives, assuming the overall demand for antitussives was not impacted long-term by the pandemic or the upregulation.

To date, this is the first analysis of opioid-containing antitussive sales in Switzerland. This study has notable strengths. The Swiss IQVIA MIDAS® data covers pharmacies, self-dispensing physicians and drugstores; the coverage in Switzerland is estimated at 100% [37]. All sales and changes for pharmaceutical specialties to pharmacies, physicians' practices and drugstores are recorded for the listed drugs. However, our database only gives information on standardised units sold and does not inform on the number of patients who acquired opioid-containing antitussives, the number of prescribers or dispensers, or their characteristics. Additionally, a comparison to other countries is difficult due to the variety of regulatory settings. While France experienced a similar upregulation of codeine-containing products from over-the-counter to prescription-only in 2017 [38], this affected not only antitussives but also codeine-containing analgesic products [39]. In France the upregulation led to a drop in overall codeine sales; however, we were unable to find any published data on the impact on antitussives specifically or on the dispensing of codeine products during the COVID-19 pan-

demic to compare it to our analysis [40]. Nevertheless, our results provide insight into the general trend observed in opioid-containing antitussive sales in Switzerland from Q1 2013 to Q3 2022.

Cumulatively, a decreasing trend was observed for the sales of opioid-containing antitussives between 2013 and 2019. It is likely that repeated media attention on cases of antitussive misuse has led to more cautious recommendation of opioid-containing antitussives in pharmacies, especially in a younger population. It does not appear that the revision of the Swiss Therapeutic Products Act in 2019 led to a further decrease in the sales of opioid-containing antitussives. However, as the COVID-19 pandemic occurred shortly following revision, longer data collection will be needed to comprehensively assess its effects on antitussive utilisation going forward.

Data availability statement

The IQVIA MIDAS[®] pharmaceutical sales data analysed for this study was licensed from IQVIA. Underlying raw data will not be disclosed, only the data points set out in this paper. The code used in the analysis can be shared upon request to the corresponding author.

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Potential competing interests

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Appendix

Table S1: Reclassification dates of opioid-containing antitussives. First and last ordinance describe the date of the issuance of the reclassification ordinance of the first product in the respective ATC class, respectively. Thirty days were added to the ordinance dates published by Swissmedic as the ordinance becomes legally binding after this period.

ATC class	First ordinance	Last ordinance
Codeine	08.05.2019	24.08.2019
Dextromethorphan	27.09.2019	27.09.2019
Opioids and expectorants	17.04.2019	24.08.2019
All	17.04.2019	27.09.2019

Table S2: Quarterly estimated sales rates (not decomposed) of opioid-containing antitussives and change compared to immediately preceding quarter. Gray cells indicate the upregulation period of the products of the respective ATC code, orange cells indicate the time of the COVID-19 pandemic in Switzerland.

	All		Codeine		Dextromethorphan		Opioids and expectorants	
Time	Sales rate	Change	Sales rate	Change	Sales rate	Change	Sales rate	Change
2013 Q1	189,859		45,189		109,151		35,519	
2013 Q2	82,851	-56.4%	23,646	-47.7%	43,345	-60.3%	15,860	-55.3%
2013 Q3	100,270	21.0%	22,675	-4.1%	54,170	25.0%	23,426	47.7%
2013 Q4	131,634	31.3%	31,423	38.6%	74,393	37.3%	25,818	10.2%
2014 Q1	133,567	1.5%	39,777	26.6%	70,611	-5.1%	23,180	-10.2%
2014 Q2	71,391	-46.6%	21,430	-46.1%	35,294	-50.0%	14,668	-36.7%
2014 Q3	91,002	27.5%	22,638	5.6%	47,853	35.6%	20,511	39.8%
2014 Q4	131,963	45.0%	33,687	48.8%	77,172	61.3%	21,104	2.9%
2015 Q1	176,112	33.5%	47,263	40.3%	103,217	33.7%	25,633	21.5%
2015 Q2	71,666	-59.3%	23,675	-49.9%	36,455	-64.7%	11,535	-55.0%
2015 Q3	94,085	31.3%	22,143	-6.5%	56,432	54.8%	15,509	34.4%
2015 Q4	125,318	33.2%	32,137	45.1%	71,955	27.5%	21,226	36.9%
2016 Q1	139,605	11.4%	34,895	8.6%	84,705	17.7%	20,006	-5.7%
2016 Q2	72,809	-47.8%	20,811	-40.4%	40,942	-51.7%	11,057	-44.7%
2016 Q3	84,121	15.5%	21,437	3.0%	49,703	21.4%	12,981	17.4%
2016 Q4	144,687	72.0%	37,778	76.2%	88,860	78.8%	18,049	39.0%
2017 Q1	142,235	-1.7%	38,438	1.7%	85,306	-4.0%	18,491	2.5%
2017 Q2	61,058	-57.1%	18,259	-52.5%	34,344	-59.7%	8,455	-54.3%
2017 Q3	83,273	36.4%	20,109	10.1%	52,303	52.3%	10,861	28.4%
2017 Q4	118,572	42.4%	30,097	49.7%	74,607	42.6%	13,868	27.7%
2018 Q1	155,492	31.1%	41,323	37.3%	96,815	29.8%	17,354	25.1%
2018 Q2	64,580	-58.5%	20,235	-51.0%	36,683	-62.1%	7,662	-55.8%
2018 Q3	78,561	21.6%	18,090	-10.6%	50,263	37.0%	10,209	33.2%
2018 Q4	118,900	51.3%	30,201	66.9%	76,114	51.4%	12,585	23.3%
2019 Q1	135,195	13.7%	38,172	26.4%	80,562	5.8%	16,461	30.8%
2019 Q2	74,116	-45.2%	27,328	-28.4%	37,471	-53.5%	9,317	-43.4%
2019 Q3	72,596	-2.1%	21,005	-23.1%	40,831	9.0%	10,760	15.5%
2019 Q4	121,269	67.0%	34,279	63.2%	73,512	80.0%	13,477	25.3%
2020 Q1	159,052	31.2%	42,026	22.6%	100,804	37.1%	16,222	20.4%
2020 Q2	23,883	-85.0%	9,341	-77.8%	11,047	-89.0%	3,494	-78.5%
2020 Q3	41,495	73.7%	14,621	56.5%	21,986	99.0%	4,887	39.9%
2020 Q4	55,973	34.9%	16,540	13.1%	33,971	54.5%	5,462	11.8%
2021 Q1	40,836	-27.0%	13,406	-18.9%	23,112	-32.0%	4,318	-20.9%
2021 Q2	40,235	-1.5%	10,449	-22.1%	25,308	9.5%	4,479	3.7%
2021 Q3	54,338	35.1%	13,566	29.8%	35,062	38.5%	5,710	27.5%
2021 Q4	102,689	89.0%	25,411	87.3%	67,812	93.4%	9,466	65.8%
2022 Q1	102,889	0.2%	30,306	19.3%	61,340	-9.5%	11,242	18.8%
2022 Q2	76,601	-25.5%	17,331	-42.8%	51,856	-15.5%	7,414	-34.1%
2022 Q3	69,105	-9.8%	18,969	9.5%	43,438	-16.2%	6,698	-9.7%

Table S3: Quarterly trend component of estimated sales rates of opioid-containing antitussives and change compared to immediately preceding quarter. Gray cells indicate the upregulation period of the products of the respective ATC code, orange cells indicate the time of the COVID-19 pandemic in Switzerland.

	All		Codeine		Dextromethorphan		Opioids and expectorants	
Time	Sales rate	Change	Sales rate	Change	Sales rate	Change	Sales rate	Change
2013 Q1	142,534		33,161		81,224		28,149	
2013 Q2	131,303	-7.9%	31,667	-4.5%	73,624	-9.4%	26,012	-7.6%
2013 Q3	120,214	-8.4%	30,262	-4.4%	66,131	-10.2%	23,821	-8.4%
2013 Q4	110,297	-8.2%	29,001	-4.2%	59,289	-10.3%	22,007	-7.6%
2014 Q1	107,023	-3.0%	28,722	-1.0%	57,106	-3.7%	21,195	-3.7%
2014 Q2	106,808	-0.2%	29,115	1.4%	57,270	0.3%	20,423	-3.6%
2014 Q3	112,285	5.1%	30,218	3.8%	61,796	7.9%	20,270	-0.7%
2014 Q4	117,820	4.9%	31,564	4.5%	66,145	7.0%	20,112	-0.8%
2015 Q1	118,777	0.8%	31,973	1.3%	67,709	2.4%	19,094	-5.1%
2015 Q2	117,961	-0.7%	31,620	-1.1%	67,937	0.3%	18,404	-3.6%
2015 Q3	112,170	-4.9%	29,768	-5.9%	64,644	-4.8%	17,758	-3.5%
2015 Q4	107,492	-4.2%	27,775	-6.7%	62,644	-3.1%	17,074	-3.9%
2016 Q1	106,155	-1.2%	27,187	-2.1%	62,361	-0.5%	16,607	-2.7%
2016 Q2	107,621	1.4%	27,855	2.5%	63,917	2.5%	15,849	-4.6%
2016 Q3	111,170	3.3%	29,371	5.4%	66,417	3.9%	15,383	-2.9%
2016 Q4	110,101	-1.0%	29,562	0.7%	65,692	-1.1%	14,848	-3.5%
2017 Q1	107,675	-2.2%	28,774	-2.7%	64,683	-1.5%	14,219	-4.2%
2017 Q2	103,859	-3.5%	27,452	-4.6%	63,001	-2.6%	13,405	-5.7%
2017 Q3	102,909	-0.9%	27,002	-1.6%	63,131	0.2%	12,775	-4.7%
2017 Q4	105,331	2.4%	27,769	2.8%	65,034	3.0%	12,528	-1.9%
2018 Q1	105,196	-0.1%	27,846	0.3%	65,006	0.0%	12,344	-1.5%
2018 Q2	104,337	-0.8%	27,464	-1.4%	64,735	-0.4%	12,138	-1.7%
2018 Q3	101,636	-2.6%	26,880	-2.1%	62,927	-2.8%	11,829	-2.5%
2018 Q4	100,470	-1.1%	27,398	1.9%	61,189	-2.8%	11,883	0.5%
2019 Q1	100,983	0.5%	28,942	5.6%	59,858	-2.2%	12,183	2.5%
2019 Q2	100,615	-0.4%	29,889	3.3%	58,260	-2.7%	12,466	2.3%
2019 Q3	103,080	2.4%	30,597	2.4%	59,993	3.0%	12,490	0.2%
2019 Q4	101,594	-1.4%	29,155	-4.7%	60,625	1.1%	11,815	-5.4%
2020 Q1	91,931	-9.5%	26,139	-10.3%	55,446	-8.5%	10,346	-12.4%
2020 Q2	78,057	-15.1%	22,724	-13.1%	46,821	-15.6%	8,512	-17.7%
2020 Q3	55,058	-29.5%	17,124	-24.6%	31,902	-31.9%	6,032	-29.1%
2020 Q4	41,253	-25.1%	13,408	-21.7%	23,364	-26.8%	4,481	-25.7%
2021 Q1	43,664	5.8%	12,929	-3.6%	26,113	11.8%	4,623	3.2%
2021 Q2	53,866	23.4%	14,548	12.5%	33,772	29.3%	5,545	20.0%
2021 Q3	69,211	28.5%	18,191	25.0%	43,981	30.2%	7,039	26.9%
2021 Q4	79,155	14.4%	20,813	14.4%	50,326	14.4%	8,016	13.9%
2022 Q1	85,679	8.2%	22,321	7.2%	54,805	8.9%	8,552	6.7%
2022 Q2	90,869	6.1%	23,774	6.5%	58,137	6.1%	8,958	4.7%
2022 Q3	96,662	6.4%	25,270	6.3%	61,977	6.6%	9,414	5.1%

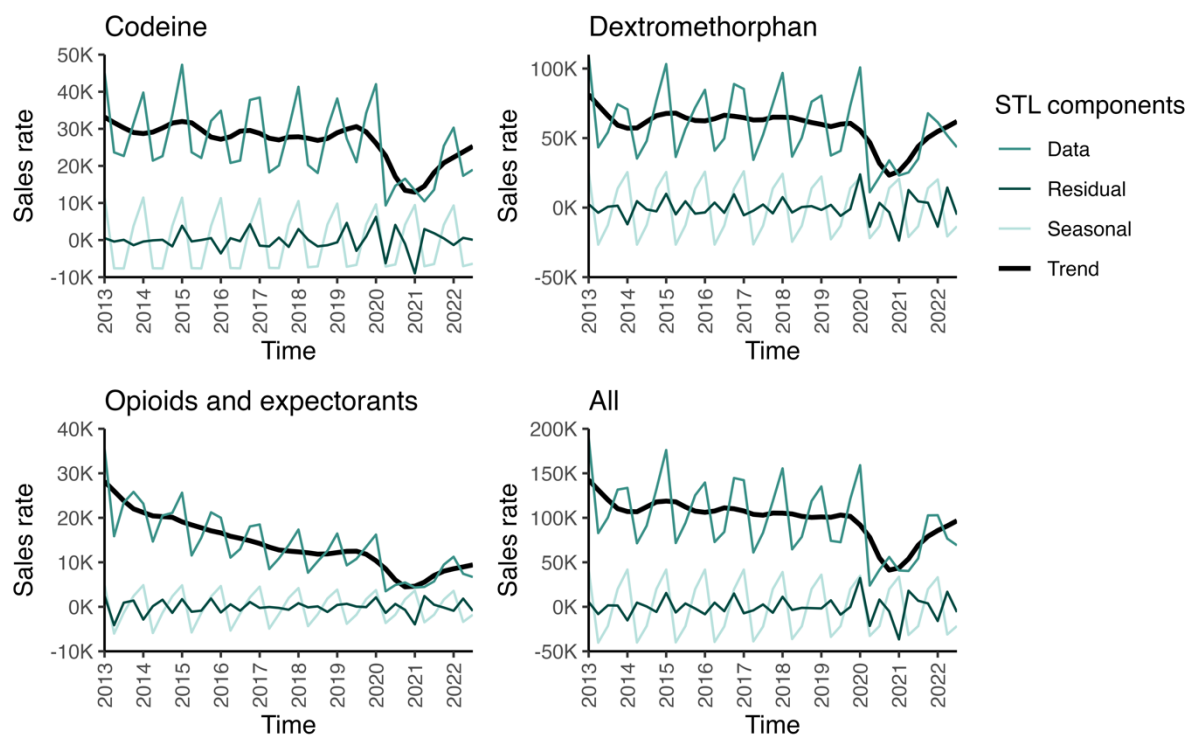


Figure S1: Plots of STL decomposed opioid-containing antitussives sales data.

Table S4: Quarterly crude rate and trend component of estimated sales rates of butamirate-containing antitussives and change compared to immediately preceding quarter. Orange cells indicate the time of the COVID-19 pandemic in Switzerland.

Time	Sales rate: crude	Change	Sales rate:trend	Change
2014 Q1	27700		14181	
2014 Q2	5044	-81.8%	15931	12.3%
2014 Q3	12804	153.8%	17791	11.7%
2014 Q4	20307	58.6%	19468	9.4%
2015 Q1	38876	91.4%	20266	4.1%
2015 Q2	5992	-84.6%	20252	-0.1%
2015 Q3	16037	167.6%	18697	-7.7%
2015 Q4	19922	24.2%	17386	-7.0%
2016 Q1	27503	38.1%	17388	0.0%
2016 Q2	6222	-77.4%	17703	1.8%
2016 Q3	17088	174.6%	18439	4.2%
2016 Q4	20830	21.9%	18655	1.2%
2017 Q1	30367	45.8%	18403	-1.4%
2017 Q2	5478	-82.0%	18287	-0.6%
2017 Q3	17125	212.6%	19044	4.1%
2017 Q4	20661	20.6%	20435	7.3%
2018 Q1	36340	75.9%	21491	5.2%
2018 Q2	9225	-74.6%	22054	2.6%
2018 Q3	21543	133.5%	21795	-1.2%
2018 Q4	21464	-0.4%	21529	-1.2%
2019 Q1	33793	57.4%	21363	-0.8%
2019 Q2	8754	-74.1%	21340	-0.1%
2019 Q3	21805	149.1%	21609	1.3%
2019 Q4	20729	-4.9%	21720	0.5%
2020 Q1	37452	80.7%	19636	-9.6%
2020 Q2	2855	-92.4%	16534	-15.8%
2020 Q3	10093	253.5%	11206	-32.2%
2020 Q4	10607	5.1%	7119	-36.5%
2021 Q1	5270	-50.3%	7540	5.9%
2021 Q2	4988	-5.3%	10015	32.8%
2021 Q3	13692	174.5%	14800	47.8%
2021 Q4	22573	64.9%	18459	24.7%
2022 Q1	26927	19.3%	22351	21.1%
2022 Q2	17005	-36.9%	26212	17.3%
2022 Q3	30554	79.7%	30278	15.5%

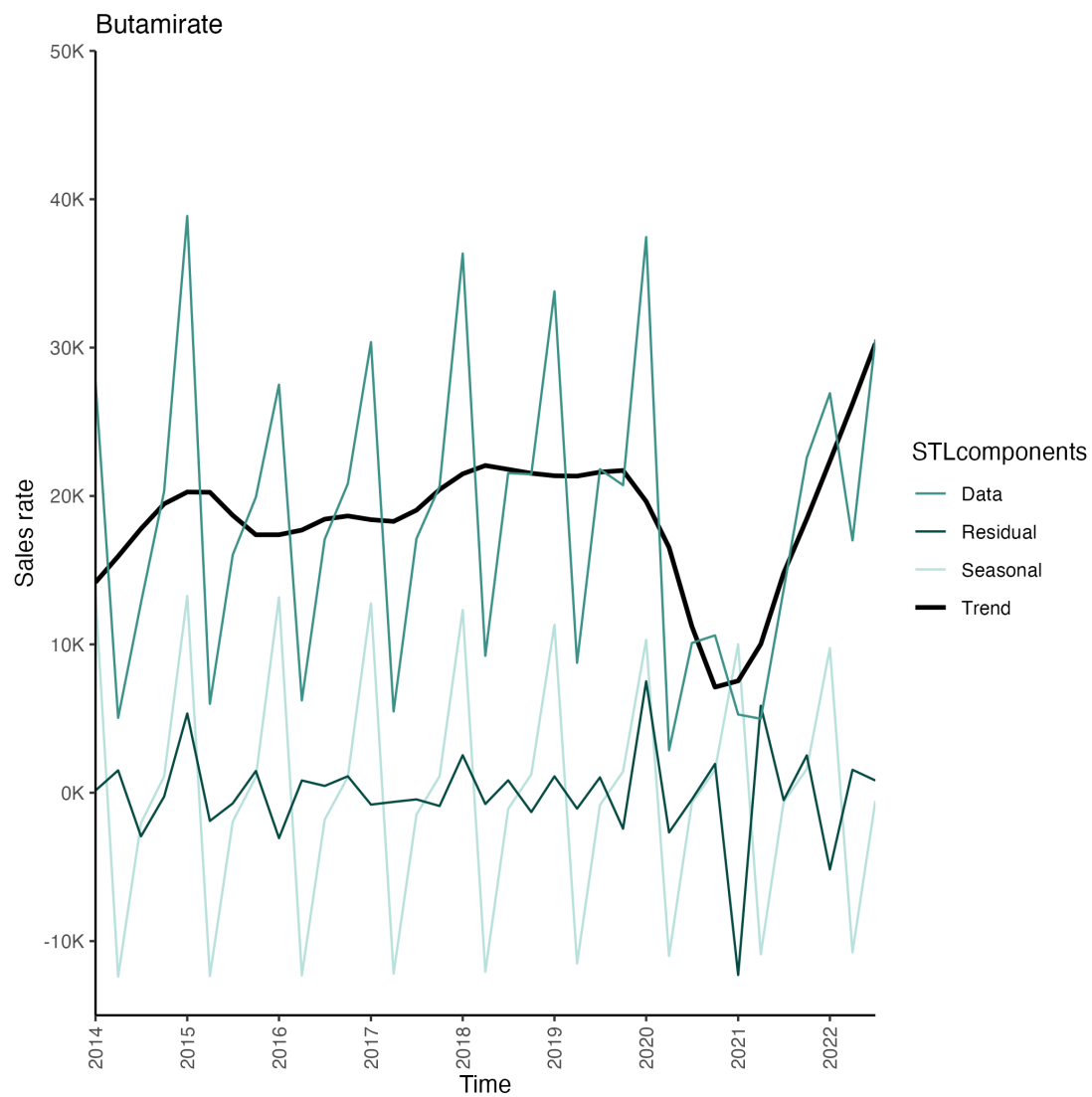


Figure S2: Plots of STL decomposed butamirate-containing antitussives sales data.