



Risperdal® CONSTA® Needle Detachment. Incidence Rates Before and After Kit Redesign: A Retrospective Study using Electronic Health Records and Natural Language Processing in the Department of Veterans Affairs

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ABSTRACT

Introduction: Janssen received reports of needle detachments for Risperdal® CONSTA® and, in response, redesigned the kit.

Objective: The study objective was to estimate the rate of Risperdal® CONSTA® needle detachments prior to and after the introduction of a redesigned kit.

Methods: This retrospective study used record abstraction in the US Department of Veterans

Affairs (VA). The 3 phases included: (1) a pilot study for methods evaluation in a sample of 6 hospitals with previously reported detachments; (2) a baseline study to ascertain the baseline detachment rate; and (3) a follow-up study to ascertain the rate for the redesigned kit. Administrative codes and natural language processing with clinical review were used to identify detachments.

Results: Pilot: we identified a subset of spontaneously reported detachments and several previously unreported events. In the baseline study (original device), from January through December 2013, 22 needle detachments were identified among 47,934 administrations of the

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drug in a census of administrations in the VA; an incidence of 0.0459%. In the follow-up study (redesigned device), from December 2015 through December 2016, there were 14 reported detachments in 41,819 injections, 0.0335%. This represents a reduction of 27% from the baseline.

Conclusion: This approach enabled us to identify needle detachments we would not have otherwise found (“solicited”). However, it likely resulted in incomplete outcome ascertainment. While this may have resulted in lower overall rates, it did not bias the comparison of the baseline and follow-up studies. The results showed that the redesigned Risperdal® CONSTA® kit reduced the incidence of needle detachment events in the VA.

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Keywords: Comparative cohort study; Department of Veterans Affairs; Electronic health records; Medical device epidemiology; Natural language processing; Needles; Pharmacoeconomics; Psychosis; Retrospective study; Risperidone; Schizophrenia; Syringe

INTRODUCTION

Background

Antipsychotic medications are given to treat schizophrenia and the manic symptoms of bipolar disorder. Schizophrenia is a chronic, severe, disabling brain disorder that affects approximately 1% of the population worldwide. It is a heterogeneous clinical syndrome with a varying constellation of signs and symptoms, including delusions, hallucinations, disorganized speech and/or behavior, and negative symptoms. Men and women are equally affected. Onset in the teens and twenties produces lifelong impairment in all areas of brain functioning, including social interactions, motivation, cognition, emotions, and senses [1, 2]. Even with treatment, most patients remain at least partially disabled. Bipolar disorder is a lifelong episodic illness that also affects about 1% of the population worldwide. It is

characterized by rapid changes in mood and behavior, which are a leading cause of disability among young people. Bipolar I disorder, which is characterized by impairing manic episodes of elevated mood and increased motor drive, also affects men and women equally [2, 3].

Typical antipsychotics target the dopaminergic system, a strategy that hasn't changed since the 1950s [4]. Atypical antipsychotics, such as risperidone, selectively inhibit dopamine D2 and serotonin receptors. Risperdal® CONSTA® is a formulation of risperidone in a long-acting injection (risperidone LAI) given every 2 weeks that is indicated for the treatment of schizophrenia and schizoaffective disorder as monotherapy and for adjunctive maintenance treatment of bipolar I disorder to delay the occurrence of mood episodes [5, 6]. Long-acting injectable antipsychotics have demonstrated improved adherence, less variability in drug plasma concentrations, and increased frequency of interaction with the treatment team, as they are administered by a clinician [6]. Risperidone LAI was first approved in Germany in 2002, then for schizophrenia in the United States in October 2003, and for bipolar I disorder in May 2009 [5].

Regulatory Background

No drug-device combination system is failsafe. In 2009, Janssen became aware of potential needle detachment issues concerning Risperdal® CONSTA®. Spontaneous reports of needle detachment were received via Janssen's worldwide spontaneous adverse event reporting and product quality complaint (PQC) systems from health care providers (HCPs) and patients. 439 reports of needle detachments were made to Janssen worldwide in the calendar year 2013. In the same year, 6,738,526 kits were distributed. Thus, the reporting rate for 2013 was 0.0065% or 65 PPM (parts per million).

As a result, Janssen made incremental improvements to the componentry in order to reduce the risk of needle detachment (Fig. 1). The development of a second-generation kit was initiated in 2011, and consisted of improvements to several device components, testing, and new instructions for use (IFU) (Fig. 2). In 2014, the second-generation kit was

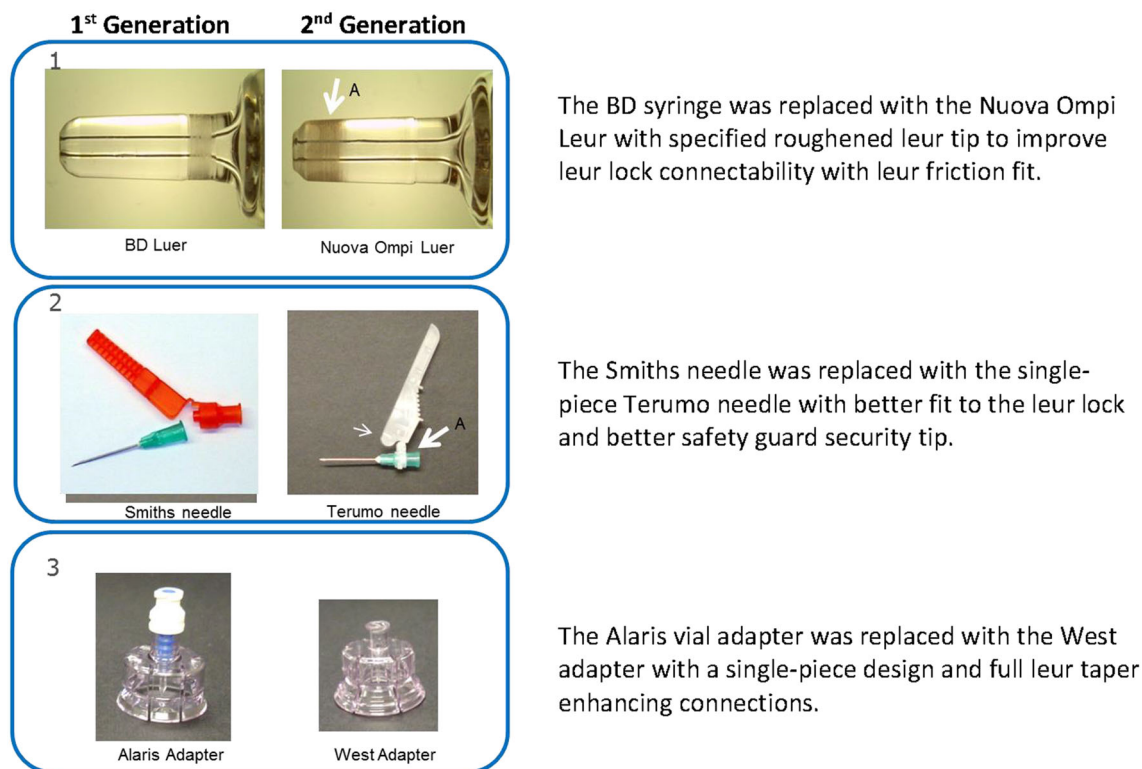


Fig. 1 Changes made to the Risperdal[®] CONSTA[®] kit

approved by regulatory authorities and introduced into commercial distribution in the US in August 2015. As of December 2015, there were no first-generation kits on the market.

Drug Product Kit Device and Improvements

Registered and approved globally, Risperdal[®] CONSTA[®] is a controlled release formulation of the drug risperidone. It is injected intramuscularly as a powder (risperidone-containing microspheres) in suspension. Four dose strengths are available in the US: 12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone per vial. The finished drug product is provided as a kit containing the following components: a vial filled with risperidone extended release microspheres for injection, a prefilled syringe containing 2 mL of diluent for reconstitution of the microspheres prior to injection, an Alaris[™] SmartSite[®] Needle-Free Vial Access Device (manufactured by CareFusion, formerly

Cardinal Health) used for vial access and powder reconstitution, a 0.9 mm × 50 mm (2-in) 20G TW gluteal injection needle with a Needle-Pro[®] Safety Device, and a 0.8 mm × 25 mm (1-in) 21G UTW deltoid injection needle with a Needle-Pro[®] Safety Device (both injection needles with the Needle-Pro[®] Safety Device are manufactured by Smiths Medical North America).

The Alaris[™] SmartSite[®] device and the injection needles with the Needle-Pro[®] Safety Device are all standard medical devices that are already marketed separately by their respective manufacturers but are included in the Risperdal[®] CONSTA[®] finished drug product kit specifically for the reconstitution and administration of the drug product. Syringe barrels, OVS (which is a German abbreviation for the Vetter tamper-evident seal) and the rubber stoppers are also externally purchased from qualified suppliers. All primary packaging materials undergo incoming release testing supported by a supplier certificate of analysis.

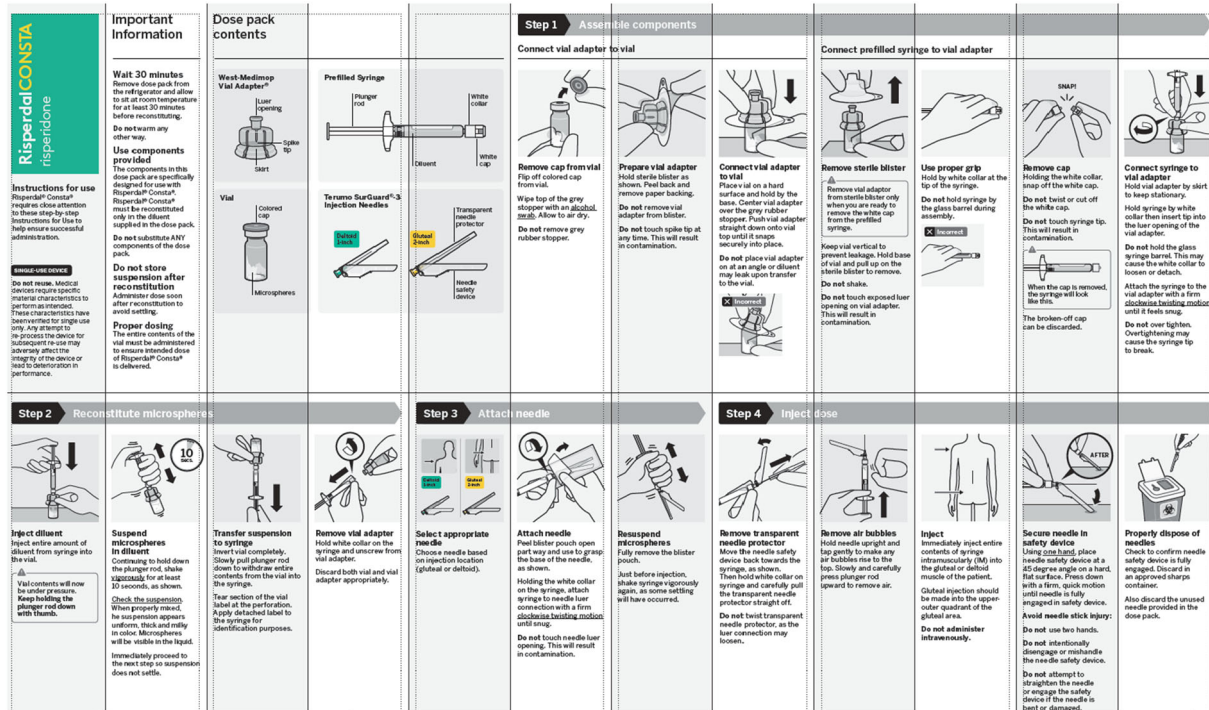


Fig. 2 Instructions for use of the second-generation kit

The Microlance[®] gluteal needle is directly shipped from Becton, Dickinson and Company Singapore to Smiths Medical (USA) for assembly into the Needle-Pro[®] Safety Device. The molded Needle-Pro[®] Safety Device is assembled with the Microlance[®] gluteal needle and then packaged into a single unit blister. The complete blister is then sterilized with ethylene oxide. A similar process is followed for the Nipro[®] deltoid injection needle. The Alaris[™] SmartSite[®] needle-free access device is supplied directly in its sterile blister to the final kit assembly packaging site. Incoming release testing of the single components and the needle blister is performed by the Global Pharmaceutical Supply Group (GPSG). The final kit packaging operation is performed at either GPSG's Ortho-McNeil packaging facility in Raritan, NJ, USA or by a contract secondary packager, Anderson Packaging in Illinois, USA. Figure 1 shows changes made from the original to the second-generation kit.

The Risperdal[®] CONSTA[®] kit consists of components that are assembled and reconstituted prior to intramuscular injection. The

administration process consists of several steps that are performed to reconstitute the drug, assemble the syringe, administer the drug, and safely dispose of the kit (Fig. 2).

Administrative Codes

Administrative codes are used to identify both the drug and administration (procedure) in electronic health records (EHRs) and medical claims data. The Healthcare Common Procedure Coding System (HCPCS) is a standardized coding system, maintained by the American Medical Association, to ensure consistent and orderly processing of healthcare claims [7]. HCPCS Level I consists of Current Procedural Terminology (CPT) using 5-digit codes to describe procedures and services provided by healthcare professionals.

HCPCS Level II, maintained and distributed by the Centers for Medicare and Medicaid Services (CMS), is used to identify healthcare products, supplies and services that fall outside the scope of CPT codes. J-codes are permanent

codes assigned to drugs administered via a route other than oral, and for chemotherapy agents [8]. J-codes were used to identify the drug used in Risperdal® CONSTA® injections.

National Drug Codes (NDCs) are universal product identifiers for human drugs and are published by the US Food and Drug Administration (FDA). These unique 3-segment codes describe the drug manufacturer, the specific product, and the package size, and are used on medical claims submitted to public and private payers [9].

The Department of Veterans Affairs (VA) serves as both provider and payer for US veterans. When care is received at a VA facility, the VA is authorized to bill third-party payers (TPPs) and pharmacy benefits managers (PBMs) to recoup the cost of care, including medication administration. The VA uses NDC codes to identify medications dispensed in these claims [10].

Medications prescribed and administered to veterans by VA providers for service-connected conditions are filled almost exclusively at VA pharmacies, and although there is no claim generated from these transactions, the medication data, including the applicable HCPCS and NDC codes, are stored in the VA electronic medical record and are accessible through the VA Corporate Data Warehouse [11].

Spontaneous vs. Solicited Reports

Spontaneous reports are made by a variety of reporters either to the company or to the FDA. Although spontaneous reporting systems are in place and routinely assessed, they do not represent actual rates of risk. There is no real denominator, number of injections in this case, with which to estimate an incidence rate. Further, spontaneous reports likely represent only a small fraction of actual events. The degree to which reporting rates reflect actual event rates is unknown.

Solicited reports, on the other hand, are systematically acquired using methods in which the sampling frame is known. Importantly, there is a reliable denominator with which to calculate the incidence rate. The rate of solicited

reports will almost certainly be higher than the rate for spontaneous reports. Wernicke et al. [12] compared spontaneous and solicited reporting rates and showed higher solicited rates. Notably, this study is based on solicited rather than spontaneous reports.

Aims

The primary aim of this study was to compare the needle detachment incidence rate for the original Risperdal® CONSTA® drug–device kit with the rate for the redesigned kit.

The objectives were to:

1. Determine the feasibility of identifying needle detachments in electronic health records (pilot study)
2. Estimate the baseline incidence rate of needle detachments for the first-generation Risperdal® CONSTA® drug–device combination kit during the calendar year 2013 (baseline study)
3. Estimate the incidence rate of needle detachments in the redesigned Risperdal® CONSTA® drug–device combination kit in the period from December 2015 through December 2016, after first-generation kits were no longer in use (follow-up study)

METHODS

Design

This was a retrospective comparative cohort study of Risperdal® CONSTA® needle detachments.

This study was conducted in 3 phases: (1) a pilot study to evaluate the methods, (2) a baseline study to establish the needle detachment incidence rate for the original kits, and (3) a follow-up study to establish the incidence rate for the redesigned second-generation kits.

An electronic health record (EHR) review was selected because there is no code for needle detachments in administrative data (i.e., claims). A detachment may be noted in the medical record text field as part of the normal documentation of care.

Participants and Setting

The study was conducted in the US Department of Veterans Affairs among patients who received at least one Risperdal® CONSTA® injection [13]. The pilot study was conducted in the 6 VA hospitals from which reports of detachments had been received (one from each hospital). The baseline study (calendar year 2013) and follow-up study (December 2015 to December 2016) cohorts were patients who had received at least one Risperdal® CONSTA® injection in the entire VA healthcare system.

Electronic health records for this study were obtained from the VA Corporate Data Warehouse (CDW) and analyzed in the VA Informatics and Computing Infrastructure (VINCI) [11, 14].

No primary patient recruitment or direct patient interaction was included in this work. This study received institutional review board (IRB) and other Veterans Affairs organizational approvals before initiation.

Intervention

The Risperdal® CONSTA® kit was redesigned and re-introduced into commercial distribution in the US in 2015. The redesign included improvements to device components and new instructions for use (Fig. 1).

Outcome

The primary outcome was the difference in needle detachment incidence rates comparing the baseline and follow-up cohorts.

Pilot Study Methods

The single goal of the pilot study was to evaluate the feasibility of the method. We compared detachments identified with the natural language processing (NLP)-assisted chart review method (solicited reports) with those obtained via the spontaneous product quality complaint (PQC) reporting system in order to answer the

question, “Can we find detachments about which we have been notified?”

Outcome Definition

Needle detachment events were identified by examining records of patients who had received at least one Risperdal® CONSTA® injection during the observation window. Both procedure and drug codes were used to identify an injection. This was followed by a NLP-assisted manual review of notes in temporal proximity to the injection.

Administrative Codes

Two sets of codes were used to identify administrations of Risperdal® CONSTA®. The National Drug Codes (NDCs; 11-digit universal product identifiers for human drugs) used were 50458-306-11, 50458-307-11, 50458-308-11, 50458-309-11, and all NDCs for Risperdal® CONSTA® (1 kit in 1 box, 2 mL in 1 syringe, 2 mL in 1 vial, provided in a dose pack containing 12.5 mg, 25 mg, 37.5 mg, and 50 mg doses) [15]. J-codes are used to report injectable drugs that ordinarily cannot be self-administered. In this study, J-2794 (injection, risperidone, long-acting) was used [8].

Natural Language Processing (NLP)-Assisted Chart Review

Natural language processing can be used to identify and extract information at a scale too large to review by hand. The accuracy of NLP varies across clinical concepts, with a higher accuracy obtained for concepts that are concrete, commonly documented, and consistently described [16]. As it was not clear how and when needle detachments would be documented, an NLP-assisted, semi-automated chart review approach was designed as an alternative to a fully automated NLP system. In this approach, potentially relevant information was selected using keywords and phrases that were then presented in a structured format to clinical annotators for review and classification.

Regular Expressions in NLP

Regular expressions (RegEx) are sequences of characters that form a search pattern in text.

RegEx is a well-established and widely used method of searching for keywords in text. It was used to represent relevant concepts in a basic root form in order to capture potential conjugations, misspellings, or variants of the word. Two lists of terms were used. If one word from the first list appeared within 25 words of any word from the second list, the statement was flagged for manual review.

Initial Regular Expression

In the pilot study, we employed a single RegEx statement to find all statements in text that could be documenting evidence of detachment or other issues related to an injection (Fig. 3).

For example, one result might include the word “needle” from the first list (found inside the first set of parentheses) and find the word “broke” from the second list (second set of parentheses) within 25 words of “needle.”

Possible detachments were identified through a multi-step process. First, we identified patterns of keywords and phrases likely to describe one of two concepts: (1) the administration of Risperdal® CONSTA® and (2) needle detachments. Each pattern list contained the root forms of words to capture any conjugations, misspellings, or variants in the text. Next, we processed all documents for patients in the cohort that were created on the date of Risperdal® CONSTA® administration, or which contained the words “risperidone,” “risperdal,” “consta,” and “injection” or any known spelling variations of these words. Statements containing at least one word from each concept list were manually reviewed by two clinical annotators. Frequently occurring duplicate statements were reviewed in groups to simplify manual review. If the reviewed statement appeared to be evidence of a PQC, the note was manually reviewed to confirm a PQC event. If any new terms and phrases were found in

relevant statements, they were added to the term lists and the process was repeated to discover new statements. Once an instance of a PQC was identified, a detailed chart abstraction of the note with the confirmed PQC was performed to extract additional information about the event and the patient.

Method Refinement

The NLP-assisted chart review was deployed on all notes 15 days prior to and 2 days after each Risperdal® CONSTA® administration in 2013 in the six pilot VA hospitals. Upon receipt of anecdotal information that PQCs could be collected and reported as infrequently as quarterly, we expanded the search window to 90 days prior to the reported PQC date. The word list for each concept was expanded based on the documented events found.

During the NLP-assisted chart review conducted for this study, new relevant words were discovered. The initial RegEx statement was found to be too slow to process a large number of documents efficiently. The word lists were split into two sets of regular expressions and a custom application was developed to identify mentions of these words in clinical notes and to determine if any of them were within 25 words of each other. Table 1 shows the expressions in each of the two sets.

In practice, the clinical notes were searched for any occurrences of words in the two sets of keywords. If a word from set 1 appeared within 25 words of a word from set 2, the statement was flagged for manual review.

In the regular expression in Table 1, the notation “\b” indicates the beginning or ending of a word, and “?” indicates that the character immediately before it appears 0 or 1 times. So “\bevents?\b” matches “event” and “events,” but does not match “prevent” or “preventing.”

```
(syringe|needle|shot|inject|inj|complication|glut|delt|intramuscular\bIM\b|butt|risper|consta)\s*(?:\W+\w+){ 0,25} \s*(fail|partial|break\b|broke|separat|disconnect|detach|dislodge|partial|full|missed|damage|crack|defect)
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Fig. 3 Regular expression terms used in the pilot study

Table 1 Revised keyword lists for the baseline and follow-up studies

Set 1	Set 2	
syringe	\bbent	Defect
needle	wrong	adverse
shot	fail	fault
inject	partial	\bevents?\b
\binj\b	break\b	\bissue
complication	broke	problem
glut	separat	complication
delt	untoward	disjunction
intramuscular	disconnect	fracture
\bIM\b	detach	breach
butt	dislodge	spill
risp	full	leak
consta	missed	drip
vial	damage	clog
plunger	crack	push
amp		
hypodermic		
hub		

The RegEx application was set to case insensitive to capture words that were capitalized and lowercase.

Record Abstraction and Adjudication

A team of clinical annotators performed chart abstraction of all notes identified through the automated approach as containing potential evidence of needle detachment. They also abstracted available relevant information about the detachment, when documented, including patient age, gender, diagnosis, site of administration, lot number, use of a second kit, detachment timing, detachment location on device, dose completeness, and role of the individual who administered injection. There is no requirement to record details about the injection (e.g., location of administration) or the kit (e.g., whether a second kit was used).

These details were reported for cases in which they were available. All identified detachments were reported as POCs in accordance with Janssen standard operating procedures.

A defined number of notes ($n = 1000$) that were identified as not containing any evidence of a potential needle detachment by the patterns and keywords were also manually reviewed to estimate the sensitivity and specificity of the automated approach. No additional detachments or potentially relevant terms were found in this review.

Baseline and Follow-Up Methods

The same methods were used for the baseline and follow-up studies. Both were conducted in the same data source. As was the case in the pilot study, Risperdal[®] CONSTA[®] injections were identified using administrative codes and health care provider notes. NLP was used to identify notes with potential evidence of detachments. Notes were reviewed by two trained clinical annotators independently to determine if potential detachments had been documented. A random sample of 1000 notes not flagged by the automated approach was reviewed to assess the specificity of the method. Data about the injection and patient characteristics were collected for needle detachment events. Figure 4 shows the process for identifying needle detachments in the VA for the baseline and follow-up studies.

The baseline and follow-up studies were based on a census of Risperdal[®] CONSTA[®] administrations in the Department of Veterans Affairs during the observation windows. That is, we did not draw a sample; we examined every administration of Risperdal[®] CONSTA[®] during the specified periods. The observed difference in needle detachment incidence rate between the baseline and the follow-up was the actual difference. No inferential statistics were required because no sampling was done.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the University of Utah IRB, the IRB of record for

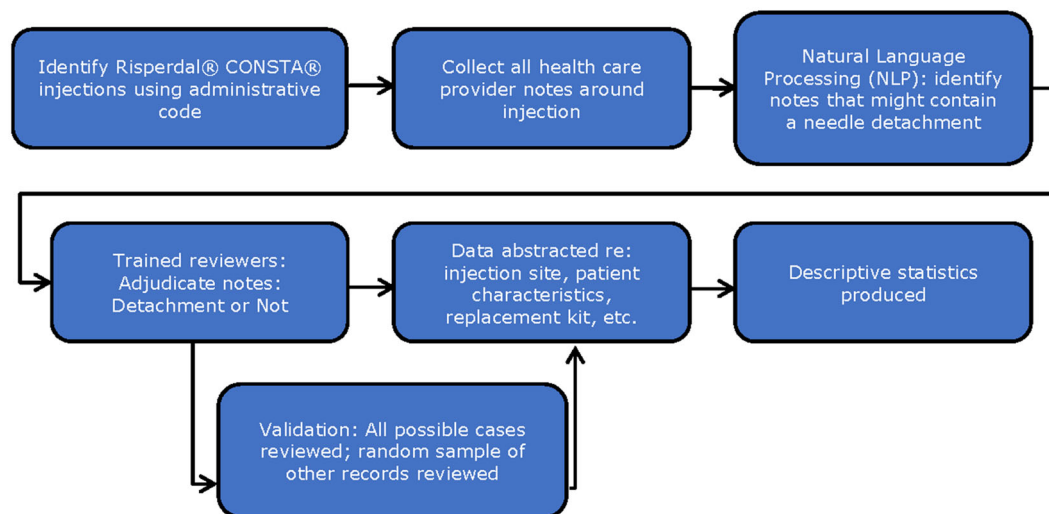


Fig. 4 Baseline and follow-up study procedure

the VA Salt Lake City Healthcare System, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The University Utah IRB waived the need for informed consent for this study. The study was also reviewed and approved by the VA Salt Lake City Healthcare System Research and Development Committee.

RESULTS

Pilot Study

Spontaneous Reports

There were 100 reports of needle detachments in the Janssen PQC database in the United States during calendar year 2013. Many of the identifiers for the reports were incomplete. Where possible, facilities were identified from addresses using Google searches with all available information. The result was 74 identifiable institutions with a known number of Risperdal® CONSTA® kits for 2013; five of those had more than one PQC report. From these results, we identified 6 sites within the VA system that had reported a needle detachment event (one at each site). Using a NLP-assisted chart review of VA electronic health records, we were able to identify three of the six spontaneously reported detachments and two additional detachments that were not in the spontaneous reports.

Patient Characteristics

As it is a health system for veterans, the VA has distinct patient demographics. In 2013, the overall patient population was largely male (93%). Nearly half (46%) of all VA patients were age 65 or older, with a median age of 62. VA patients were 73% white, 16% black, and 5% Hispanic [17].

The patient population in the baseline study (calendar year 2013) was largely male (91%), consistent with VA demographics. Nearly two-thirds (65%) of the patients receiving Risperdal® CONSTA® were between the ages of 45 and 64, with a median age of 56, slightly younger than the overall patient population. Only 55% were white, compared with 73% of the overall patient population. The majority of the patients (59%) had a diagnosis of both schizophrenia and bipolar disorder. Patients in the follow-up study were slightly older at 57 years, closer to the median in the VA population. The proportions of the patients who were male (91%) and white (56%) were similar to those in the baseline study. The follow-up study had slightly smaller proportions of patients with schizophrenia only (29% vs. 32%) or with schizophrenia and bipolar disorder (55% vs. 59%), but slightly higher proportions of patients diagnosed with bipolar disorder only

Table 2 Patient characteristics for US Department of Veterans Affairs

Baseline: calendar 2013 Follow-up: Dec 2015–Dec 2016	Baseline		Follow-up	
	N	%	N	%
	3608	100%	3008	100%
Age				
< 18 years	0	0.0%	0	0.0%
18–34 years	405	11.2%	308	10.2%
35–44 years	391	10.8%	344	11.4%
45–54 years	890	24.7%	545	18.1%
55–64 years	1431	39.7%	1128	37.5%
65–74 years	425	11.8%	612	20.3%
≥ 75 years	66	1.8%	71	2.4%
< 65 years	3117	86.4%	2325	77.3%
≥ 65 years	491	13.6%	683	22.7%
Median	55.7		57.2	
Mean (sd)	53.4 (12.0)		55.0 (12.9)	
Gender				
Male	3286	91.1%	2740	91.1%
Female	322	8.9%	268	8.9%
Diagnoses*				
Schizophrenia only	1146	31.8%	876	29.1%
Bipolar disorder only	234	6.5%	290	9.6%
Schizophrenia and bipolar disorder	2136	59.2%	1655	55.0%
Neither diagnosis	92	2.5%	187	6.2%
Race				
White	1973	54.7%	1677	55.8%
Black	1361	37.7%	1097	36.5%
Asian	34	0.9%	32	1.1%
Native Hawaiian or Pacific Islander	40	1.1%	38	1.3%

Table 2 continued

Baseline: calendar 2013 Follow-up: Dec 2015–Dec 2016	Baseline		Follow-up	
	N	%	N	%
American Indian or Alaskan native	33	0.9%	25	0.8%
Unknown	167	4.6%	139	4.6%
Ethnicity				
Hispanic	291	8.1%	218	7.2%
Unknown	3317	91.9%	2790	92.8%
Census region**				
Northeast	595	16.5%	468	15.6%
Midwest	757	21.0%	669	22.2%
South	1582	43.8%	1365	45.4%
West	573	15.9%	438	14.6%
US Territory	101	2.8%	68	2.3%

*Schizophrenia defined as ICD9 diagnosis codes 295.xx and v11.0. Bipolar defined as ICD9 diagnosis codes 296.xx except for 296.90 and 296.99. All codes must have occurred on or before the date of the first administration of Risperdal® CONSTA® in the study period.

**Census region defined based on the zip code of where care was provided during the first administration of Risperdal® CONSTA® in the study period

(9.6% vs. 6.5%) or with neither schizophrenia nor bipolar disorder (6.2% vs. 2.5%) (Table 2).

Risperdal® CONSTA® Administrations

There were 47,934 administrations of the drug to 3608 patients who had at least one clinical note in the baseline; and 41,819 administrations to 3008 patients in the follow-up (December 2015–December 2016). The number of clinical notes examined in the baseline study was 204,116; this number was 159,361 in the follow-up study (Table 3).

Table 3 Risperdal[®] CONSTA[®] administrations and health care provider notes

	Baseline		Follow-up	
	<i>N</i>	<i>N</i> patients	<i>N</i>	<i>N</i> patients
Injections				
Administrations of Risperdal [®] CONSTA [®] with clinical note	47,934	3608	41,819	3008
Clinical notes				
Total # of any clinical notes	652,102	3608	490,175	3008
Total # of relevant clinical notes	204,116	3608	159,361	3008

Needle Detachments

Twenty-two (22) needle detachments were identified in the VA system in 2013; 0.046% of the 47,934 Risperdal[®] CONSTA[®] administrations. A majority of these needle detachment events were deltoid injections ($n = 14$), which resulted in a partial ($n = 12$) or missed ($n = 3$) dose. In at least half of the cases, a second kit was used. In the ten cases in which a lot number was recorded (12 were missing a lot number), seven unique lot numbers were found (Table 4).

In the follow-up study, 14 needle detachments were identified in 41,819 administrations of Risperdal[®] CONSTA[®] from December 1, 2015 through December 31, 2016; 0.033% of the administrations of the drug. This is a reduction of 27% from the baseline rate of 0.046% (Table 5). Half of the detachments occurred during deltoid administrations ($n = 7$). Ten [10] resulted in a partial ($n = 4$) or missed ($n = 6$) dose. Among the seven cases in which a lot number was recorded, all were distinct.

None of the 1000 randomly selected notes not initially flagged by the automated approach contained evidence of a detachment.

LIMITATIONS

This method was likely subject to incomplete outcome ascertainment due to needle

detachments that were not recorded in the medical record. This may have resulted in an incidence rate that is lower than the true rate.

CONCLUSION

This study was based on solicited rather than spontaneous reports. This is a strength of the present study design that cannot be obtained with spontaneous reports because solicited reports are systematically acquired using methods in which the sampling frame is known. In this case, we searched all occurrences of Risperdal[®] CONSTA[®] injections documented in electronic health records for the occurrence of likely needle detachments, rather than relying on spontaneous reports made to the company or the FDA.

While this may be a better representation of the rate than spontaneous reports, it is still likely a conservative estimate resulting in incomplete outcome ascertainment. This may have resulted in incidence rates that are lower than the true rate. However, it would not bias the comparison of the baseline and follow-up because the same methods were used for both.

In the pilot study, we identified a subset of the spontaneously reported detachments and identified several previously unreported events. The most plausible explanation for finding only a subset of the spontaneous reports is that some

Table 4 Risperdal® CONSTA® needle detachments

	Baseline		Follow-up	
	N	%	N	%
% of injections	22	0.046%	14	0.033%
% of patients	22	0.59%	14	0.45%
Location of administration				
Deltoid	14	63.6%	7	50.0%
Gluteal	2	9.1%	1	7.1%
Unknown	6	27.3%	6	42.9%
Lot number				
Known	10		7	
Unknown	12	54.6%	7	50.0%
2nd kit used?				
Yes	11	50.0%	4	28.6%
No/unknown	11	50.0%	5	35.7%
			5	35.7%
Detachment timing				
Before injection	5	22.7%	4	28.6%
During injection	11	50.0%	5	35.7%
After injection	0	0.0%	0	0.0%
Unknown	6	27.3%	5	35.7%
Detachment location				
Needle detached*	14	63.6%	4	28.6%
Vial adapter detached	6	27.3%	5	35.7%
Both detached	0	0.0%	0	0.0%
Unknown	2	9.1%	5	35.7%
Dose completeness				
Full	2	9.1%	2	14.3%
Partial	12	54.6%	4	28.6%
Missed	3	13.6%	6	42.8%
Unknown	5	22.7%	2	14.3%
HCP administering dose				
Medical doctor	1	4.6%	0	0.0%
Physician assistant	0	0.0%	0	0.0%
Nurse practitioner	0	0.0%	0	0.0%
Nurse	1	4.6%	2	14.3%
Unknown	20	90.9%	12	85.7%

Table 5 Results summary

	Detachments	Injections	Proportion	PPM	PPM reduction	% Reduction
Baseline (2013)	22	47,934	0.000459	459		
Follow-up (Dec 2015–Dec 2016)	14	41,819	0.000335	335	124	27.0%

events had not been included in the clinical notes accompanying the injection. Anecdotal reports from interviews with healthcare providers suggested that only a portion of detachments are recorded in the text field. While it is likely that both the baseline and follow-up studies captured the majority of detachments recorded in the clinical notes, there may have been needle detachments that were undocumented and perhaps unreported; missed by both solicited and spontaneous reporting systems. At present, there is no way to quantify the number of detachments that were missed by this method or that do not appear in spontaneous reports. However, there is no reason to assume that there was bias in the incomplete outcome assessment from the baseline to follow-up studies. So, while the rate is likely underreported, an assessment of the change from baseline to follow-up remains unbiased.

RELEVANCE

The results showed that the redesigned Risperdal® CONSTA® kit reduced the incidence of needle detachment events in the Department of Veterans Affairs. Replication of this study in other data sources will be important for generalizing the findings. These results were obtained using NLP-assisted electronic medical record review, a method that may prove useful in other settings.

Further work may involve identifying needle-stick injuries to health professionals. This was not included in the present study because information about needle-stick injuries to health professionals is generally not recorded in the patient records and requires complex institutional approvals.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the University of Utah IRB, the IRB of record for the VA Salt Lake City Healthcare System, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The University Utah IRB waived the need for informed consent for this study. The study was also reviewed and approved by the VA Salt Lake City Healthcare System Research and Development Committee.

Data Availability. The datasets for these analyses are not publicly available due to policies and the regulation of data governed by the Department of Veterans Affairs. Future analysis of the data can be coordinated with the VA authors on reasonable request.

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REFERENCES

- McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev.* 2008;30:67.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. (DSM-5™). Washington, DC: American Psychiatric Association Publishing; 2013.
- Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet.* 2016;387(10027):1561–72. [https://doi.org/10.1016/S0140-6736\(15\)00241-X](https://doi.org/10.1016/S0140-6736(15)00241-X) (Epub 2015 Sep 18).
- Javitt DC. Twenty-five years of glutamate in schizophrenia: are we there yet? *Schizophr Bull.* 2012;38(5):911–3.
- Janssen Research & Development, LLC. Company core data sheet for risperidone (LAI), version 23 (dated 17 Feb 2015). Raritan, NJ: Janssen Research & Development, LLC.; 2015.
- Bobo WV, Shelton RC. Risperidone long-acting injectable (Risperdal® CONSTA®) for maintenance treatment in patients with bipolar disorder. *Expert Rev Neurother.* 2010;10(11):1637–58. <https://doi.org/10.1586/ern.10.143>.
- Centers for Medicare & Medicaid Services. HCPCS—general information. Baltimore, MD: Centers for Medicare & Medicaid Services; 2019. <https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/index.html?redirect=/MedHCPCSGenInfo/>.
- Centers for Medicare & Medicaid Services. Healthcare Common Procedure Coding System (HCPCS) Level II coding procedures. Baltimore, MD: Centers for Medicare & Medicaid Services; 2011. <http://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/HCPCSLevelIICodingProcedures7-2011.pdf>. Retrieved on April 21, 2015.
- US FDA. National Drug Code Directory. Silver Spring, MD: US FDA; 2019. <https://www.fda.gov/drugs/informationondrugs/ucm142438.htm>.
- Smith M, Joseph G. Pharmacy data in the VA health care system. *Med Care Res Rev.* 2003;60(3):92S–123S. <https://doi.org/10.1177/1077558703256726>.
- Fihn SD, Francis J, Clancy C, Nielson C, Nelson K, Rumsfeld J, Cullen T, Bates J, Graham GL. Insights from advanced analytics at the Veterans Health Administration. *Health Aff (Millwood).* 2014;33(7):1203–11. <https://doi.org/10.1377/hlthaff.2014.0054>.
- Wernicke JF, et al. Detecting treatment emergent adverse events in clinical trials. *Drug Saf.* 2005;28(11):1057–63.
- VA Office of Health Equity. National Veteran Health Equity Report FY 2013. Washington, DC: US Department of Veterans Affairs; 2016. https://www.va.gov/HEALTH/EQUITY/docs/National_Veterans_Health_Equity_Report_FY2013_FINAL_508_Comp.pdf.
- DuVall SL, Nebeker JR. VINCI: a convergence of policy and technology for enabling big data analytics in the Department of Veterans Affairs. In: IBM Canada Software Laboratory Centre for Advanced Studies Research 22nd Annual International Conference; 2012 Nov 5–7; Toronto, Canada.
- US FDA. National Drug Code Directory. Silver Spring, MD: US FDA; 2015. <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.html>. Retrieved on April 21, 2015.
- Uzuner O, Solti I, Cadag E. Extracting medication information from clinical text. *J Am Med Inform Assoc.* 2010;17(5):514–8. <https://doi.org/10.1136/jamia.2010.003947>.
- National Survey on Drug Use and Health (NSDUH) by the Substance Abuse and Mental Health Services Administration (SAMHSA). Past year prevalence of any mental illness among US adults (2016). Rockville, MD: NSDUH; 2016. <https://www.nimh.nih.gov/health/statistics/prevalence/any-mental-illness-ami-among-us-adults.shtml>.