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Title: Kluver-Bucy syndrome following traumatic brain injury: A systematic synthesis and review of

pharmacological treatment from cases in adolescents and adults

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Conflicts of Interest

The last author (MH) has given talks on this topic for which travel and accommodation has been paid by the organisers. In addition, he has accepted fees for consulting and research from the pharmaceutical companies: Servier, Bionomics, Novartis, Eli Lilly and Lundbeck. All other authors declare no known conflicts of interest.

Abstract

Kluver-Bucy syndrome (KBS) is a rare clinical presentation following traumatic brain injury (TBI). Symptoms include visual agnosia, placidity, hyperorality, sexual hyperactivity, changes in dietary behavior, and hypermetamorphoses. Objectives: To identify and synthesize the available evidence from case reports and case series on the treatment profile of KBS in adolescents and adults post-TBI. Method: Four bibliographic databases MEDLINE OVID, EMBASE, PsycINFO, SCOPUS were searched for relevant literature. No date or language restrictions were applied. All case reports containing original data on KBS following TBI in adolescents and adults were included. Articles were evaluated and data extracted according to predefined criteria. *Findings*: The literature search identified 24 case reports of KBS post-TBI published between 1968-2017. Most cases were male (70.1%) and the mean age at injury was 25.1 years, range 13-67 years. Injury to one or both temporal lobes occurred in most of cases. In appropriate sexual hyperactivity was the most common KBS symptom followed by a change in dietary behavior and hyperorality. Visual agnosia was the least reported. In 50% of cases, the patient fully recovered from KBS. Half of the cases described pharmacological management, the most common medication prescribed being carbamazepine (CBZ). Overall there was a lack of data available on pharmacotherapy initiation and duration. *Discussion*: The complex presentation of KBS presents challenges in terms of treatment options. While overall cases that were prescribed CBZ had positive outcomes, due to the reliance on case reports, it is difficult to make a definitive recommendation to guide clinical practice.

Background

Kluver-Bucy syndrome is a rare neuropsychiatric disorder that can occur following traumatic brain injury (TBI). First described in 1937 as an experimental neurobehavioral syndrome in monkeys with bitemporal brain lesions (1); both transient (2) and permanent KBS in humans (3) has been subsequently observed. The syndrome is characterized by complex behaviors including placidity, visual agnosia, altered sexual activity, hyperorality, memory disorders, hypermetamorphosis and emotional and nutritional behavior changes (4-6). Psychological status in those with KBS depends not only on the extent and location of the lesion, but also on the level of emotional and intellectual development prior to the injury and the extent of social stimulation following brain damage. Diagnosis of KBS does not require all symptoms to be manifested simultaneously and fully symptomatic KBS is rare (3, 6, 7).

Kluver-Bucy syndrome is usually associated with lesions of the amygdala or amygdaloid pathways. It has been reported in patients displaying a variety of pathologies including herpes simplex encephalitis (8), Huntington's disease (9), Alzheimer's disease (10), Adrenoleukodystrophy (11), heat stroke (12), meningitis (13), multiple sclerosis (14), Pick's disease (15), temporal epilepsy (16), and Reye's syndrome (17). These neurological disorders are associated with destruction or dysfunction of bilateral mesial temporal lobe structures (7).

There are currently no definitive KBS treatment recommendations. KBS symptoms are managed on a symptom by symptom basis as opposed to pharmacotherapy being prescribed for KBS as a whole.

Given the rare presentation of KBS in both clinical practice and the academic literature, our understanding of KBS following TBI has primarily relied on case reports due to the lack of available higher quality data. The French SOFMER (French Physical Medicine and Rehabilitation Society) guidelines for the care management of behavioral disorders following TBI report Level 4 Grade C evidence for treatment with carbamazepine (CBZ) based on the experience of four patients with post-traumatic lesions localized bitemporally that developed KBS (18). For the four patients in the case series, the article reports that several symptoms responded dramatically

to CBZ (19, 20). The symptoms were not specified. However, of the four patients, two had head injuries of indeterminate origin (19, 20). The guideline concluded that CBZ is a useful agent in the treatment of this unusual syndrome.

To build upon the findings reported in the SOFMER guidelines with a more comprehensive review of case reports, the initial objective of this systematic review was to use case reports to describe KBS in adolescents and adults who have sustained a TBI. The second objective was to compare and contrast individual case reports for patients with KBS post-TBI where prescription of pharmacotherapies is reported. Given the potential impact of developmental issues in children, this review will focus on adolescents and adults. While a small number of reviews have considered KBS following TBI (7, 21), as far as we are aware, KBS following TBI has not been the focus of a systematic review.

This review forms part of a larger project to synthesize the evidence for the pharmacological management of neurobehavioural symptoms post TBI as a prelude to the development of a clinical guideline. This systematic review in addition to academic and clinical expert consensus will contribute towards the development of evidence based recommendations for the pharmacological management of complex neurobehaviours including KBS in patient's post-TBI.

Method

Prior to commencing the review, we searched the PROSPERO and Joanna Briggs Database to ensure the proposed work was not duplicating any work currently in progress. This systematic review is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Inclusion and exclusion criteria

The present review was limited to case reports and case series of human subjects available as full-text articles. Case reports/series of adolescents and adults (aged 13 years and above), both males and females who had sustained a TBI displaying partial or full KBS symptoms were considered for inclusion. Traumatic brain injury was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Studies were included regardless of the severity of the injury or mechanism of injury. Participants with penetrating and non-penetrating head injury were eligible for inclusion.

The following are considered characteristic KBS symptoms (6).

1. Placidity: Loss of normal anger or fear

2. Hyperorality (tendency to explore objects within the mouth)

3. Visual agnosia (inability to recognize objects without loss of gross visual discrimination)

4. Hypermetamorphosis (tendency to attend and manipulate objects within the visual field)

5. Indiscriminate dietary behavior including hyperphagia (an excessive insatiable appetite)

6. Hypersexuality

Diagnosis of the full form of the syndrome is based on the occurrence of all the aforementioned symptoms (6). Diagnosis of the partial form of the syndrome requires the presence of 3 or more symptoms (4, 6). Studies where diagnosis of KBS was based on fewer than 3 symptoms were excluded from the review.

To be included, case reports were required to show medical evidence of TBI; that is, unequivocal TBI documented in medical records or other health/medical reports cited by the research team associated with the published article. Examples of unequivocal evidence include findings from brain imaging (e.g. CT scan, MRI), Glasgow Coma Scale (GCS) score, post traumatic amnesia (PTA) and loss of consciousness.

Studies in a language other than English were included if a translation service was available to the researchers. The following studies were excluded: case reports/series of children up to the age of 13 years, case reports/series where the mechanism of injury was not clearly stated and it was therefore not possible to conclude that TBI was the focus and case studies based on self-report of TBI from either the individual or an informant, in the absence of other medical evidence regarding the head injury as outlined above.

A description of the syndrome post-TBI focusing on demographic and injury characteristics, brain imaging, symptoms and pharmacotherapy will be provided. The outcomes that are the focus of this review are treatment effectiveness as measured by resolution or improvement in KBS symptoms, overall recovery and harms including adverse events resulting from prescribed pharmacotherapy.

Search Strategy

The search strategy was developed based on the PICO (Population, Intervention, Comparator, Outcome) elements of relevance to this review (P= Kluver-Bucy syndrome secondary to TBI). It included a range of Medical Subject Headings (MeSH) terms and key words linked by Boolean operators. The searches were carried out on December 20, 2016 and repeated on November 5, 2017. Terms were modified as appropriate for each database. The following databases were searched with no date, age or language limitation: MEDLINE: OVID SP interface; EMBASE: Excerpta Medica Database, PsycINFO: OVID SP interface; SCOPUS. The Medline search terms and number of results for each database is included in Appendix 1.

To ensure the search was as comprehensive as possible, the formal search of bibliographic databases was supplemented with searches of Google scholar and ResearchGate. We also carried out electronic searching of the following online journals: Brain Injury, Neuropsychology, Journal of Neurotrauma, Neurocase and BMJ Case reports. Reference lists and bibliographies of retrieved articles were reviewed to identify research not located through other search strategies. Finally, we asked colleagues if they were aware of any case reports in this area.

Study Selection

Results from the four database searches were downloaded into Endnote X7 and de-duplicated. Titles and abstracts were screened by two independent reviewers (FC, AK) against the inclusion and exclusion criteria for the review. Studies that potentially met the inclusion criteria at the title and abstract stage were retrieved in full and independently assessed against the inclusion criteria by two members of the review team (FC, AK). An article could be included in the review if it contained at least one relevant case. Articles which included both relevant cases and cases that did not meet the inclusion criteria, for example due to patient age or KBS not being secondary to TBI were still eligible. Discussion between reviewers was used to achieve agreement over the eligibility of two studies. Full text studies that did not meet the inclusion criteria were excluded and reasons for exclusion are provided in Figure 1.

Assessment of Methodological Quality

Quality was assessed by three reviewers (FC, AK, DL) using the Joanna Briggs Institute critical appraisal eight question checklist for case reports. In brief, the questions assess the quality of reporting of the patient's demographic characteristics, current clinical condition, diagnostic tests or assessment methods, interventions or treatment, post intervention clinical condition, harms and unexpected consequences and take-home lessons.

Data Extraction

Where available, the following data were extracted from the included case reports using a customized data extraction tool pilot tested on two case reports of KBS secondary to herpes simplex virus (FC, AK). Minor modifications to the data extraction tool were made following the pilot. To aid interpretation of data, we sought to ensure that one of the reviewers involved in data extraction had a medical degree (AK). The specific data items extracted where available are listed below.

- Country of case; age, gender and mechanism of injury of the case and report of Loss of Consciousness, Glasgow Coma Scale score, Coma

- Study population - traumatic brain injuries (injuries other than to the head, time post-injury)

- Kluver-Bucy syndrome symptoms, whether KBS was full or partial, time of KBS onset, duration of KBS

- Imaging: Computed Tomography (CT) /Magnetic Resonance Imaging (MRI)

- Pharmacotherapy intervention if used including type of pharmacological compound, dose, frequency and duration, co-interventions and their details

- Outcomes and when they were measured

- Treatment response and treatment adverse events.

Results

Study selection

The search strategy resulted in an initial yield of 388 references from four bibliographic databases. Seven potentially relevant references were identified from Google Scholar. After removal of duplicates, 236 references remained. Of these, 185 references were excluded based on either title or abstract.

The full text of 51 articles was retrieved for detailed evaluation; after independent review by two authors (FC, AK), 32 articles did not meet the inclusion criteria. Primary reasons for exclusion included incorrect study design (not a case report) or population out of scope (studies of children or animals, KBS secondary to conditions other than TBI). One study published in Italian was translated by a graduate student. One potential case report published in Polish was excluded following translation by a staff member. An English version for a further paper published in Polish was available therefore the Polish version was excluded. After independent review, 19 articles referring to 24 case reports met inclusion criteria for the review. The search strategy is provided in Figure 1.

Data Synthesis

The findings of the 24 cases are presented as a narrative descriptive synthesis structured around the individual case report characteristics, injury severity, brain imaging, KBS symptoms, use of pharmacotherapy and treatment outcomes.

Demographics

The included case reports were published between 1968 and 2017. Half of the case reports (n=12) were from the USA with the remainder from India (n=2) (22, 23), Turkey (n=1) (24), Japan (n=1) (25), Italy (n=1) (26), Poland (n=4) (19, 20, 27) and the Netherlands (n=3) (28). Of the included case reports, 70.1% related to males (n=17). The mean age at injury for the 21 case reports specifying age was 25.1 years with a range of 13-67

years. Three further reports specified either early twenties or late twenties (7, 29). The most common mechanism of injury was road traffic accident (n=17, 70.1%). There were three case reports following gunshot (7, 35, 36) and two each following a fall (19, 20, 32) or sport related accident (7, 33). Table 1 reports the demographic, brain imaging and injury characteristics of the included case reports.

Injury severity

Half of the cases had sustained a severe head injury, as defined by Glasgow Coma Scale score (GCS) of < 8, coma and recorded loss of consciousness (LOC). Duration of LOC was reported in only one case report. The GCS was recorded in 13 reports with nine cases recording a GCS < 8. Coma was documented in three case reports (25, 26, 34). There were four cases where loss of consciousness was noted but the GCS was not provided. In three cases, injury severity was unavailable as no information on GCS, coma or loss of consciousness was reported (22, 35, 36).

Brain imaging

Brain imaging (MRI/CT) was available for most of the cases (n=23). Lesions were most commonly found in the temporal lobes, with temporal lobe lesions noted in 18 (90%) cases. Of the 15 cases (75%) with lesions isolated to the temporal lobes only, 11 showed bilateral lesions and two cases had unilateral lesions (left n=1; right n=1). The frontal lobes were involved in four cases. In three of these cases, the temporal lobes were also involved.

Kluver-Bucy syndrome symptoms

Sexual hyperactivity or inappropriate sexual behavior was the most common KBS symptom noted in 95.8% of the case reports (n=23). A change in dietary habits to hyperphagia or bulimia was reported in 20 cases, with hyperphagia being the most common presentation (13 cases). Hyperorality occurred in 17 cases and hypermetamorphoses was present in 13 cases. Placidity was reported in 15 cases. For some of these cases, the placidity occurred intermittently with agitation and aggression. Visual agnosia was the least common KBS

symptom, with only eight cases reporting visual agnosia. Full and Partial KBS is based on the number of presenting KBS features; in the majority of included cases the KBS was partial (n=19, 79.1%), with the remainder being full (n=5, 20.9%) (6, 23-25, 31).

With respect to associated clinical findings, seizures were reported in four cases and problems with memory were reported for 16 cases. Challenging behaviors associated with KBS including impulsivity, recalcitrance, agitation and aggression – often extreme was noted in 16 cases.

In the majority of cases, KBS symptoms appeared early post-TBI, for 12 cases this occurred in under seven days post-TBI and for five cases between 7 and 31 days post-TBI. No cases of KBS were diagnosed during coma or where a period of stupor was described (25). Symptoms of KBS appeared around six months post-TBI for one case (34), one year post-TBI for two cases (22, 28) and two years post-TBI for one case (28). For 2 cases it was not possible to determine the time of onset. Table 2 outlines the KBS features including time of onset and associated clinical findings for each of the included case reports.

Recovery over time – all cases (n=24)

Response to treatment and improvement in Kluver-Bucy features is outlined in Table 4. Of the case reports included in this review, mention of recovery from KBS was noted in 22 cases (two cases did not report on recovery). In the 11 cases that showed positive improvement in all presenting KBS symptoms, the duration of KBS ranged between 7 days and 14 months. In other cases where there was partial symptom improvement (n=6) some KBS symptoms fully resolved while other persisted long term. For five cases, there was no improvement with reports of a deterioration in health and a reduced capacity for functioning (19, 26, 28). A single case reported progressive deterioration of symptoms leading to death (26). There was underreporting of when KBS patients were assessed over the timeline of their hospital stay, rehabilitation and following discharge. The assessment of long term outcomes of 12 months or longer post-TBI were recorded in a minority of cases (n=5) (19, 20, 25, 28).

Pharmacological Treatment

Pharmacological management was documented in 50% of the case reports (n=12). Pharmacological management with Carbamazepine (CBZ) was the most commonly reported intervention (n=10). The use of first-generation antipsychotics was noted in three case reports. Selective serotonin reuptake inhibitors (SSRIs) were prescribed in three cases. The prescription of two or more medications is noted in four case reports (7, 27, 29). Table 3 provides details of the post-acute pharmacological management. Only two case reports reported duration of treatment at 4 years, with the remaining case reports not reporting duration of medication(s) treatment.

Treatment with Carbamazepine

The age range of patients who received either CBZ or another anticonvulsive medication was 16-39 years old. In 10 of the 12 cases where pharmacological treatment was described, CBZ was used to manage patients presenting with either full or partial symptoms of KBS. In these cases, the dose of CBZ ranged from 400mg to 1000mg per day (19, 20, 27, 29, 32, 34, 35). Therapeutic drug monitoring to tailor CBZ treatment was only described in three cases and aimed to reach serum levels between 6 -11 ug/ml. In most cases, CBZ was used as monotherapy whereas in two cases CBZ was combined with propranolol and haloperidol respectively which resulted in resolution of all or the majority of symptoms (7, 27, 29). Unfortunately, few of the case reports described any data on the adverse effects of any drugs that were used in symptom management.

Response to Pharmacological treatment – 12 cases

Half of the case reports (n=12) included in this review described pharmacological management. Of these, six cases were associated with a positive improvement in symptoms; with some reporting complete resolution of symptoms and return to preinjury activities. Partial improvement was reported in three cases with some KBS symptoms improving over time and others persisting. In the two definitive TBI cases reported by Goscinski *et al* that had a long follow-up of 3 and 25 years, prolonged psychiatric symptoms persisted with reduced capacity for functioning (19, 20). In 50% of the cases that reported administration of carbamazepine, a positive

improvement in KBS symptoms was noted. In two cases, a combination of drugs was used that did not include CBZ but; sertraline, thiothixene, bromocriptine, topiramate, haloperidol, propranolol and quetiapine (7, 29). Both case reports note a gradual improvement in symptoms specifically relating to agitation.

Methodological quality

The methodological quality of each case report was examined according to the Joanna Briggs Institute critical appraisal for case reports template. The questions that form the basis of the critical appraisal are included in appendix 1. Overall there was clear reporting of the patient's demographic characteristics (Question 1) current clinical condition (Question 3), and diagnostic tests or assessment methods (Question 4). Only 13 case reports (54.1%) clearly described the patient's history in a timeline by providing information on past medical history and relevant family history (Question 2) and only seven case reports provided information on harms and unexpected consequences (Question 7). Table 5 summaries the critical appraisal findings for the included KBS cases.

Discussion

To the best of our knowledge, this is the first systematic review to identify and synthesize the evidence for KBS secondary to TBI from case reports. Using a defined search strategy applied to four bibliographic library databases, 24 case reports were identified that met the inclusion criteria and form the focus of this review. Notwithstanding the methodological limitations associated with case reports, given the rarity of KBS and the lack of studies with higher quality methodologies; the use of case reports offers opportunities to better understand KBS post-TBI.

In the current review, hypersexuality, hyperorality and aggressive behavior were the most common presenting KBS symptoms. Visual agnosia was the least common symptom. Gerstenbrand *et al*, 1983 summarized their experiences with posttraumatic cases of KBS reporting clinical data on 40 cases diagnosed between 1978 and 1981 (37). While no individual case data was presented, the frequency of KBS symptoms was reported. Symptoms of bulimia, memory disturbances, hyperorality and visual agnosia occurred in 30 cases. Hypersexuality occurred in 18 cases and aggressiveness in 11 cases. Persistence of hypersexuality at one year was noted in 12 cases, bulimia in 8 cases and aggressiveness in 10 cases. While the sources of the cases are not described, the majority were male (77.5%) and the age range indicates the cohort were younger as children were included [aged 7-33 years (mean 17.2 years)]. The differences may reflect the heterogeneous nature of TBI. It is unclear whether the patients in the study by Gerstenbrand *et al*, 1983 had traumatic brain injury or other acquired brain injury (37). Six cases died within 10 weeks of their accident so it is possible that the cases described in the current review were less serious.

While the natural history of KBS post-TBI is not known (23), it appears as a chronic persistent state in some patients and a transient resolving state in others (6). Of the case reports described in the current review, the majority of cases showed partial or full recovery. For the majority of cases, the course of KBS ranged from 5 days to one year. For other cases (n=8), the syndrome was ongoing 1-25 years following onset depending on

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when the patient was evaluated.   While it cannot be ruled out that this reflects a positive-outcome publication bias, the extent of recovery is consistent with the study by Formisano et al, 1995 who examined the global outcome of 19 patients with KBS secondary to severe brain injury following a traffic accident. To be included in the Formisano study, cases were counted as KBS if they had two of the KBS symptoms (38). This is at odds with the definition of partial KBS which requires three symptoms (6). While no individual case data was presented, of the 19 included KBS patients, four did not regain independence; six achieved family integration and nine work integration. In keeping with Formisano et al, 1995 (38); lesions in the temporal lobes were common in the case reports included in the current synthesis.

The nature and anatomic location of the lesions necessary to produce human KBS post-TBI has not been definitively determined, in part, due to the limits of current routine structural imaging. Investigators have proposed a number of hypotheses. Goscinki *et al*, 1997 proposed a bilateral injury of the mediobasal temporal lobe as a result of swelling or edema of the brain and compression of the arteries (19,20). Yoneoka *et al*, 2004 hypothesized that KBS symptomatology may reflect edema induced transient dysfunction of the right temporal and basal frontal lobes (25). Slaughter *et al*, 1999 proposed combinations of posterior frontal and anterior temporal lobe defects (29) and Deginal and Changty postulated disruptions of pathways connecting the dorsomedial thalmi with prefrontal cortices and other limbic areas (23). Notably, the extent of neurological deficits do not correlate with the level of personality disturbances (27). More recently, Caro *et al* 2011 proposed that KBS results from mesiotemporal lesions or other changes (possibly transient) leading to hypofunctioning in the amygdalae or its projections regardless of etiology (7). In the case of transient KBS, they propose that the disappearance of KBS symptoms follow improvement in the localized neuronal dysfunction.

A secondary objective of the current review was to compare and contrast the individual case reports that described pharmacological management of KBS related symptoms. The French SOFMER guidelines on drugs for behavioural disorders following TBI, reports Level 4 Grade C evidence for the use of CBZ (18). This is based on a single case series of four patients treated with CBZ (19, 20). No data on duration of treatment or timepoint at which treatment was initiated was provided. Dose of CBZ was not reported for Case 1. They report that the patients showed improvement as measured by the Glasgow Outcome Scale (GOS) at discharge, three and six months after trauma when given CBZ during hospitalization and after discharge (19, 20). Case 2 did not show a change in GOS. The nature of the improvement was not described. Given the complexity of the syndrome, that only two cases can be definitively considered as TBI, the lack of pharmacological information and lack of reporting on which symptoms improved, guideline recommendations based on this article should at best be circumspect. Ten case reports that describe treatment with CBZ are included in this review providing some additional evidence on the use of CBZ in relation to KBS. Improvement of symptoms was seen within three weeks of commencing CBZ (22) and in one case, complete resolution of symptoms was reported (34) but no time frame specified. Other cases reported general improvements in symptoms in patients taking CBZ but again no time frame was mentioned when improvements occurred (23, 27, 34, 35).

Carbamazepine is a carboxamide derivate antiepileptic drug with a chemical structure similar to tricyclic antidepressants and is used in the management of seizure disorders, neuropathic pain and psychiatric disorders (39). The efficacy of carbamazepine as an anticonvulsant drug has been demonstrated in patients with temporal lobe epilepsy (40) with additional symptoms similar in nature to KBS which could be one of the reasons behind its use. Moreover, both full and partial remission of symptoms following CBZ treatment has been noted in KBS associated with a range of aetiologies other than TBI. Unfortunately, the case reports in the current study do not report in detail which of the diagnostic KBS symptoms improved or not. Improvements in behavioural, hyperorality and cognitive symptoms were documented.

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Of the 24 cases described in this systematic review, ten were treated with CBZ. Overall, the cases suggest that CBZ may be an effective treatment for certain symptoms of KBS. Of the cases treated with CBZ, a serum CBZ trough level of > 6µL/mL was reported in three patients (optimal therapeutic range 4-12 µl/mL). Due to its potentially severe toxic effects (e.g. ataxia, seizures, dystonic reaction, and up to coma), it is crucial to avoid CBZ overdosing (39). While a serum trough level of 6µL/ml is still within the recommended range, the lack of effect with CBZ in Slaughter case 1 (29) maybe associated with a subtherapeutic trough level. The antipsychotic drug chlorpromazine usually shows a high sedative effect and increase potential for extrapyramidal symptoms. In the case presented by Hooshmand, chlorpromazine (41) may have been given as a treatment for psychotic symptoms and then potentially switched to CBZ for long-term seizure management (34). In terms of effectiveness, the early introduction of CBZ seems to be important as stated by Gozinski et al, 1997.

The prescription of multiple medications was described in four cases. In Slaughter case 2, both lorazepam and valproic acid was prescribed (34). Lorazepam is usually prescribed for its anxiolytic effects and its reported pharmacokinetic interaction with valproic acid might lead to further aggravated sedative effects (42). In Slaughter case 1, the patient received several antidepressants including sertraline and trazodone (29). Sertraline was later substituted with fluoxetine; both drugs are SSRI's. Some KBS symptoms have obsessive compulsive disorder (OCD) features and sertraline at higher doses has been shown to be effective with OCD (43). However, sertraline and fluoxetine are both metabolised on common cytochrome P_{450} pathways including CYP2D6 and pharmacokinetic interactions might be expected in the present case given the rapid succession (44). The antidepressant trazodone, a potent serotonin and α1-adrenergic receptor antagonist and weak serotonin reuptake inhibitor(50) was administered together with CBZ. With CBZ being a known inducer of CYP3A4, potential interactions might be clinically relevant and exacerbate symptom remission (46, 47).

It is important to acknowledge that this systematic review is subject to limitations that are a feature of case reports. As case reports are retrospective observational studies, causal inference cannot be made. There is a risk of positive-outcome bias and they may over interpret features of the case due to the different emphasis

given by authors to cases. For the current review, data was missing for some of the collected attributes. Underreporting of when KBS patients were assessed during their hospital stay, rehabilitation and following discharge limits the interpretation of the duration of KBS symptoms. Being a natural experiment, the case cannot be repeated and the care of patients with KBS may have changed over the years. As peer reviewed articles on Kluver-Bucy syndrome are not very common, the search strategy did not include a large range of terms and it is possible that relevant cases were missed. We think the likelihood of this is small given the range of databases searched; reference lists consulted and search of Google scholar.

Notwithstanding this, the strengths of the review include the systematic identification of cases using a specified search strategy and a critical appraisal of the reports quality. Moreover, no date or language restrictions were applied and we were able to get three studies translated. The review brings together 24 cases of KBS post-TBI of which half were treated with pharmacotherapy. By doing so it helps clinicians to understand the clinical spectrum of KBS post-TBI and may offer guidance in the personalization of treatments in clinical practice.

Conclusion

This systematic review has identified and synthesized the evidence from 24 case reports of KBS syndrome post-TBI. The case reports demonstrate the complex presentation of Kluver-Bucy syndrome symptoms post-TBI. Treatment with CBZ was associated with improvement in KBS symptoms in seven out of ten cases. However, given the quality of evidence it is not possible to make a practice recommendation in the clinical guideline under development with any degree of certainty. Whether this intervention is trialed for a patient relies on the individual clinical presentation, lack of response to other treatments and clinical indication.

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Table 1: Demographic and injury features of post-TBI Kluver-Busy syndrome cases (n=24)

First author	Case	Age at injury	Sex	Country	Mechanism	Loss of consciousness	Glasgow coma score*	Brain MRI/CT findings
Aygun (24)		29	M	Turkey	RTA	No LOC.	GCS=14	Contusions of bilateral temporal lobes.
Bhat (22)		30	M	India	RTA	N/R	N/R	Mild R anterior temporal gyrus atrophy.
Caro (7)		Late twenties	M	USA	SPORT	No LOC		Increased size of frontal lobes. R parietal white matter lesions. Inferatentorial lesions in cerebellar hemispheres.
Deginal (23)		16	M	India	RTA	Yes LOC.	GCS=10	Bilateral temporal contusions with edema.
Fiume (26)		23	M	Italy	RTA	Coma#		Imaging not done. Craniotomy subtemporal.
Goscinski (19-20)	1	23	M	Poland	RTA	Yes LOC.	GCS=4	L subdural hematoma. R-sided cerebral edema.
Goscinski (19-20)	2	67	M	Poland	FALL	Yes LOC.	GCS=7	Intracerebral bitemporal haematoma.
Hardy (2)		16	M	USA	GUN	No LOC		R temporal lobe lesion.
Hooshmand (34)		16	F	USA	RTA	Yes LOC. Coma		R temporal lobe damage.
Isern (31)		37	F	USA	GUN	No LOC		Bitemporal lobe damage.
Kwiatwoski (27)	1	16	M	Poland	RTA	Yes LOC.	GCS=3	Bilateral contusions: temporal and parietal lobes. Haemorrhage into subcortical nuclei. Paracerebral hematoma.
Kwiatwoski (27)	2	16	F	Poland	RTA	Yes LOC. GCS=3		L temporal subdural haematoma. R hemisphere haemorrhagic contusion and cerebral edema.
Lilly (6)		57	M	USA	RTA	Yes LOC		Bilateral damage to inferior temporal lobes.
Morcos (32)		39	M	USA	FALL	Yes LOC		Inferior L temporal damage.
Moviat (28)	1	13	F	Netherlands	RTA		GCS<7	L-sided parietal subdural hematoma. Generalised oedema. Loss of basal cisterns. L temporal + R frontotemporal contusions.
Moviat (28)	2	13	F	Netherlands	RTA		GCS=7	L-sided parietal subdural hematoma Generalized oedema.

								Loss of basal cisterns. Bilateral frontotemporal contusion.
Moviat (28)	5	14	N	Netherlands	RTA	GCS=7		R frontotemporal hematoma. R frontal atrophia. Hypodensity L thalamus.
Salim (48)		24	F	USA	RTA	No LOC.	GCS=14	Focal axonal injury to L temporal lobe.
Slaughter (29)	1	Late twenties	M	USA	RTA	Yes LOC.	GCS=3T^	L intraparenchymal haematoma, subarachnoid haemorrhage. L temporal lobe contusions. Bilateral enlargement -temporal horns.
Slaughter (29)	2	Early twenties	M	USA	RTA	Yes LOC.	GCS=6	Bilateral small frontal lobe contusions.
Smigielski (36)		25	F	USA	RTA	N/R	N/R	Bilateral temporal lobe contusions. L-sided frontal injury.
Stewart (35)		20	M	USA	RTA	N/R	N/R	Bilateral frontal and temporal encephalomalacia.
Yoneoka (25)		17	M	Japan	SPORT	Yes LOC. Coma		R-sided acute subdural haematoma with transtentorial herniation.
York (30)		25	M	USA	GUN		GCS=5T^	Bifrontal and temporal lobe contusions.

Table 1, Legend: R=right, L=left, C=Case, F =Female, M=male, GCS=glasgow coma score, LOC= Loss of consciousness, RTA=road traffic accident, MRI=Magnetic Resonance Imaging, CT=Computed Tomography, N/R= Not reported, * On admission unless stated otherwise #no LoC or GCS reported. ^T tube inserted so verbal responses not assessed

Table 2: Kluver-Bucy syndrome symptoms and features (+ = symptom occurred, N= symptom not described).

First author	Case	Time of KBS onset*	Memory	Visual Agnosia	Placidity	Change in diet	Hyperoral	Sexual Hyperactivity	Hyper Metamorphoses	Behaviour	Full/Partial KBS
Aygun (24)		T1	N	+	+	+	+	+	N	FA	Full
Bhat (22)		T3	N	+	+	N	+	+	+	FA	Partial
Caro (7)		T5	N	N	+	+	+	+	N	A	Partial
Deginal (23)		T2	N	+	+	+	+	+	+	A	Full
Fiume (26)		T1	+	N	+	+	+	+	+	D	Partial
Goscinski (19,20)	1	T2	+	N	N	+	+	+	N	A/FA	Partial
Goscinski (19,20)	2	T2	N	N	N	+	+	+	+	A	Partial
Hardy (2)		T1	+	+	+	+	N	+	+	FA	Partial
Hooshmand (34)		T3	+	N	N	+	+	+	N	A	Partial
Isern (31)		T1	+	+	+	+	+	+	+	A	Full
Kwiatwoski (27)	1	T1	N	+	+	+	+	+	N	A	Partial
Kwiatwoski (27)	2	T1	+	N	N	+	+	+	+	A/D	Partial
Lilly (6)		T2	+	+	+	+	+	+	+	FA/R	Full
Morcos (32)		T1	+	N	N	+	N	+	+	A	Partial
Moviat (28)	1	T4	+	N	+	+	N	+	+	RE	Partial
Moviat (28)	2	T3	+	N	+	N	N	+	+	RE	Partial
Moviat (28)	5	T1	+	N	+	+	+	+	N	RE	Partial
Salim (48)		T1	+	N	+	+	N	+	N	A	Partial
Slaughter (29)	1	T2	+	N	N	+	+	+	N	A/R	Partial
Slaughter (29)	2	T1	+	N	N	N	+	N	N	A/FA/R	Partial
Smigelski (36)		T5	N	N	N	N	+	+	N	A	Partial
Stewart (35)		T1	+	N	+	+	N	+	+	A	Partial

Yoneoka (25)		T2	N	+	+	+	+	+	+	N/R	Full
York (30)		T1	+	N	N	+	N	+	N	N/R	Partial

Legend: Symptoms of Kluver-Bucy as outlined Lilly et al (11), *T1 =Less than 7 days post-TBI, T2= 7-31 days post-TBI, T3= 31-365 days post-TBI, T4= >than 1 year post-TBI, T5= not able to be determined, FA=Flat effect, RE=Recalcitrance, R=Restlessness, D=Disoriented, A=Agitation or Aggression. Yr=year, yrs=years, mths=months

Table 3: Pharmacotherapy for post-TBI. Kluver-Bucy syndrome cases (n=12) following initial treatment in the acute setting

Author	Case	Pharmacotherapy
Bhat (22)		Carbamazepine no further details provided
Caro (7)		Valproate changed to topiramate, quetiapine, propranolol, benztropine, haloperidol
Deginal (23)		Carbamazepine, 200 mg b.i.d
Goscinski (19,20)	1	Carbamazepine
Goscinski (19,20)	2	Carbamazepine 400mg b.i.d
Hooshmand (34)		Chlorpromazine 300mg/per day - stopped Carbamazepine 1000mg/per day – commenced following Chlorpromazine
Kwiatwoski (27)	1	Haloperidol Carbamazepine. 3 x 200mg. per day. 6ug/ml serum level
Kwiatwoski (27)	2	Carbamazepine, 3 x 200 mg per day. 6ug/ml serum level
Morcos (32)		Carbamazepine 400mg b.i.d
Slaughter (29)	1	Carbamazepine 600mg per day, Propranolol – no change in baseline behaviour Trazodone Sertraline titrated to 150mg. Substituted with Fluoxetine 40mg morning, 20mg noon
Slaughter (29)	2	Haloperidol then substituted with Olanzapine Lorazepam, Valproic acid, Thiothixene, Bromocriptine Sertraline 150mg/per day
Stewart (35)		Carbamazepine serum levels 9-11ug/ml for 3 weeks, then 8-9ug/ml for one year

Legend: b.i.d= twice a day, mg=milligram, ug=microgram, ml=milliliter

Table 4: Response to treatment for post-TBI Kluver-Bucy syndrome cases

Author	Case	KBS Symptom improvement	Duration of KBS	Response/Outcomes to treatment
Aygun (24)		Positive	Five days	Complete improvement
Bhat (22)		Positive	Three weeks	Asymptomatic
Caro (7)		Partial		Gradual improvement in behaviour and cognition
Deginal (23)		Partial		30% improvement in behaviour and KBS symptoms when measured at 8 weeks post-TBI
Fiume (26)		No improvement	death	Progressive deterioration leading to death
Goscinski (19,20)	1	No improvement	ongoing	7 years: Reduced intellectual capacity and functioning, 25 years: irritable, verbally aggressive, poor memory, apathy, no libido
Goscinski (19,20)	2	No improvement	ongoing	Prolonged psychiatric disorders, social maladaptation, aggression and self-harming
Hardy (2)		Partial	15 days	Improved appetite, language, no sexual comments at 15 days post TBI OCD and blunt affect persisted
Hooshmand (34)		Positive	1 year	Seizures over in 24 hours. Hyperorality disappeared. Concentration improved. Substantial improvement in memory
Isern (31)		Not reported	4-5 months	
Kwiatwoski (27)	1	Positive		Managed to effectively return to his pre-accident situation including work
Kwiatwoski (27)	2	Partial		Persisted symptoms of hyperorality 4 years post-TBI Improvement in dietary habits, emotional dullness, emotionality, physical violence, anger management.
Lilly (6)		Positive	1 month	
Morcos (32)		Not reported		
Moviat (28)	1	No improvement		No change in 6 years rehabilitation
Moviat (28)	2	No improvement		No change in 3 years rehabilitation
Moviat (28)	5	Partial	2 years	bilateral pyramidal signs improved, No change in 3 years rehabilitation,
Salim (48)		Positive	~7 days	Resolved
Slaughter (29)	1	Positive	3.5 months	Complete resolution
Slaughter (29)	2	Positive	18 days	Reduced symptoms of agitation/lip chewing. Symptoms never recurred
Smigelski (36)		Positive	8 months	Impressive neurobehavioural and neurocognitive recovery
Stewart (35)		Positive	<3 months	Positive improvement (gradual decrease, then ceased violent attacks)
Yoneoka (25)		Positive	14 months	Transient symptoms of KBS. Returned to high school and then college

York (30)		Partial		Improvement in residual memory and cognition.

Legend: KBS= Kluver-Bucy syndrome, C= case, Partial=Partial improvement in symptoms, OCD=obsessive compulsive disorder

Table 5: Critical appraisal of Post-TBI Kluver-Bucy syndrome case reports according to the Joanna-Briggs Institute appraisal checklist for case reports.

Author/Year	Case	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Aygun (24)		Y	Y	Y	Y	Y	N/A	N	Y
Bhat (22)		Y	Y	Y	Y	Y	Y	N	Y
Caro (7)		Y	Y	Y	Y	Y	Y	Y	Y
Deginal (23)		Y	Y	Y	Y	Y	Y	N	Y
Fiume (26)		Y	N	Y	Y	N	N	N	N
Goskinski (19, 20)	1	Y	N	Y	Y	N	N	N	Y
Goskinski (19, 20)	2	Y	N	Y	Y	N	N	N	Y
Hardy (2)		Y	N	Y	Y	N	Y	N	N
Hooshmand (34)		Y	Y	Y	Y	Y	Y	Y	Y
Isern (31)		Y	Y	Y	Y	Y	Unclear	N	N
Kwiatwoski (27)	1	Y	Y	Y	Y	Y	Y	N	Y
Kwiatwoski (27)	2	Y	Y	Y	Y	Y	Y	N	Y
Lilly (6)		Y	N	Y	Y	Y	Y	N	Y
Morcos (32)		Y	Y	Y	Y	Y	Y	N	Y
Moviat (28)	1	Y	N	Y	Y	N	N	Y	Y
Moviat (28)	2	Y	N	Y	Y	N	N	Y	Y
Moviat (28)	5	Y	N	Y	Y	N	N	Y	Y
Salim (48)		Y	N	Y	Y	N/A	N	N	Y
Slaughter (29)	1	Y	Y	Y	Y	Y	Y	Y	Y
Slaughter (29)	2	Y	N	Y	Y	Y	Y	Y	Y
Smigelski (36)		Y	N	Y	Y	N	Y	N	N
Stewart (35)		Y	Y	Y	Y	Y	Y	N	Y
Yoneoka (25)		Y	Y	Y	Y	Y	Y	N	Y
York (30)		Y	Y	Y	Y	N	N	N	Y

Legend: C=case, Y = meets criteria, N=does not meet criteria, N/A = not applicable

Figure 1

Figure 1 flow diagram:

Search Results
4 Databases (n=388)
Other sources (n=7)

Total (n=395)

After duplicates removed (n= 236)

Excluded based on title or abstract (n=185)

Full text papers (n=51) independently evaluated by 2 authors

Articles excluded based on eligibility criteria (n=32)

- KBS secondary to other conditions (n=18)
- Diagnosis of KBS only 2 symptoms (n=1)
- Brain injury of indeterminant cause (n=2)
- Wrong age group (children) (n=4)
- Editorial (n=1)
- Not related to KBS (n=3)
- Foreign language unable to be translated (n=2)
- Animal study (n=1)

Included articles (n=19) covering 24 case reports