

Can medication management review reduce anticholinergic burden (ACB) in the elderly? Encouraging results from a theoretical model

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ABSTRACT

Background: Review of recent journal articles and various relevant current textbooks provides strong evidence to show that anticholinergic burden is a material issue in frail and at-risk patients. This study assesses the anticholinergic burden in a group of patients in residential care facilities and then applies a theoretical intervention model. It is based on a scoring system known as the Anticholinergic Cognitive Burden (ACB) scale, and attempts to reduce the anticholinergic burden while maintaining therapeutic benefits.

Methods: A database of 691 patients was analyzed for each individual's ACB based on the scale of scoring produced by groups of experts in the area. A theoretical intervention was then conducted using relevant, evidence-based practice guidelines for clinical therapeutics in Australia. The intervention had the aim of reducing the total ACB without affecting the apparent intended effectiveness of the prescribed therapy.

Results: Of the 35% ($n = 242$) patients who score at least 1 point on the ACB, a reduction is achievable in 59% of the cases. In particular, the reduction from a clinically significant score of 3 or above to 2 or below for 49 of those patients is possible in 85% of the cases. Overall, this represents a reduction from 7.10% to 1.01% for the entire population. It is also found that of the 246,960 counts of items dispensed (both prescription and non-prescription) for these patients, 47,334 (or 19.2%) of these were of agents on the ACB scale.

Conclusions: The study found that it appears to be possible that the total ACB of a group of 691 patients can be significantly reduced.

Key words: ACB, anticholinergic agents, anticholinergics, cognitive burden, reduction

Introduction

Nearing the end of the second decade of life, the human body would have reached its full potential development, up to and including cognitive functions and maturation of the central nervous system (CNS). It is from this point that it reaches the stage of inevitable decline, which continues until death (Hutchison and O'Brien, 2007). This aging process is often accompanied by diminishing bodily and overall physiological reserve. It is worth noting that the trend and rate of functional reserve decline differs greatly between individuals, hence there are always variations in any sample population (Rockwood *et al.*, 2011).

Frailty – what does it mean to be “frail”?

Frailty is not an easy concept to define. Most experienced clinicians can and do correctly identify “frail” patients who come into their care, although this would be considered mostly instinctive. The challenge then lies in finding the definitions for, and quantifying the level of frailty.

The problems arise when researchers look for factors to include or exclude in an appropriate sample group (Rockwood, 2005; Rockwood and Mitnitski, 2007). Traditionally, the focus of frailty lies in the measure of patients' abilities in cognition, continence, mobility, and function. These are relatively simple parameters to measure and give reasonable predictive validity (Davis *et al.*, 2011). It should be emphasized that, although there is a positive correlation between advancing age and frailty, they are *not* dependent variables of each other (Rockwood and Mitnitski, 2011). Patients who are frail are particularly predisposed to the unwanted effects of systemic anticholinergic agents. This may include delirium, xerostomia, visual disturbance, and

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iatrogenic impairment of cognitive function, such as short-term memory.

Some patients of advancing age may require assistance to the extent that they need multiple daily dosing of their medications put into clearly labeled slots on disposable devices. Such devices, labeled as “Days of the Week” and time slots (e.g. breakfast, lunch, and dinner time), allow patients or their carers or nursing staff in aged care facilities to administer the medication and keep track of compliance. Such systems may be known as “dosing administration aids” (DAA).

Anticholinergics – Why are they targeted?

It is established that a frail individual (at least from pharmacokinetics perspective) should be treated differently from their non-frail counterparts (Agar *et al.*, 2009). This is especially the case with medications possessing anticholinergic effects. In this section, sample medications will be used to demonstrate how anticholinergics affect the frail in a manner that differs from the effects on “normal 25-year-old Caucasian male” (Abe *et al.*, 2009), in which so many phase-1 trials of medications are performed. Some of these medications may be used for their anticholinergic properties for the desired action, but these are also often associated with side effect profiles (Nishtala *et al.*, 2009).

Which medications are most frequently implicated?

Authors in this field tend to assign an artificial value as a means of quantifying the predicted anticholinergic impact of these medications (Carnahan *et al.*, 2006). The numbers are usually between 0 and 3, with zero being “no anticholinergic activities,” and 3 being the highest single contributor to the anticholinergic burden.

The top medications (but by *no means* limited to) that are implicated through a review of no fewer than six articles (Tune *et al.*, 1992; Carnahan *et al.*, 2006; Boustani *et al.*, 2008; Minton *et al.*, 2009; Fox *et al.*, 2011; Hori *et al.*, 2011), by class, in descending order of impact and frequency of prescription are as follows:

1. Tricyclic antidepressants (e.g. amitriptyline, doxepin),
 2. some “typical” antipsychotics (e.g. trifluoperazine),
 3. some SSRIs (e.g. paroxetine),
 4. atropine*
- (*not frequently used clinically, but it is often used as a benchmark for standardized scores/levels reflecting anticholinergic activities).

The cumulative anticholinergic burden considered clinically significant is 3 or greater. For ex-

ample, amitriptyline on its own would satisfy that requirement, as will a combination of amantadine and atenolol, or a triple combination of frusemide, metoprolol, and digoxin (a *very* commonly used combination for congestive heart failure; Krum and Teerlink, 2011).

What do they do to the frail patient?

One notable feature of anticholinergic “burden” (*unwanted* anticholinergic activity is often referred to as “burden” by the researchers in this area) is the effect on the CNS (Hori *et al.*, 2011). Hori *et al.* (2011) compared two groups of Alzheimer’s disease patients with possible other co-morbidities who were hospitalized, and distinguished the two sample groups as “with serum anticholinergic activity (SAA) burden” and “without SAA burden.” When they compared the performance in the Mini-Mental State Examination (MMSE), for example, the groups that were free of SAA burden outperformed their counterparts by a margin of over 48% (13.16 vs. 8.89, $p = 0.0367$). Delirium and behavioral disturbance was also significantly differentiated between the groups, with margins sometimes as large as three-fold compared with burden-free subjects. For the purposes of this study, however, dosage adjustments were *not* part of the scope, and therefore no consideration was given to the dosage, method of delivery, or “doubling-up” of both in any one patient’s medication regimen. In other words, any one agent will only attract a single score on the total ACB (e.g. oxybutynin given in *both* oral and transdermal forms will attract the score of 3 *once*).

Prevention and minimization

From the perspective of clinical pharmacy, the focal basis of practice appears to be one of prevention rather than “cure” (Spinewine *et al.*, 2007). Home Medication Review (HMR), in its current form in Australia, is based upon two basic elements – optimizing the medication regime by aligning medical practitioners’ prescribing habits with best evidence, and improving adherence by patient consultation and counseling. Both of these elements are proven to be effective in reducing hospital admission and overall cost to the public health system from a *general* perspective (Desborough *et al.*, 2011; Maidment *et al.*, 2012). The other reason would be the quality of life for those patients. It is often associated with self-empowerment and independence, and this can only be achieved by preventing and minimizing the need for hospital admission and stay. This approach also reduces the possible compounding of the problem, as it is found, the ACB in a large number of patients actually *increased* after discharge from hospital (Wawruch *et al.*, 2012).

Table 1. Summary of characteristics of patients studied

NUMBER OF PATIENTS	AGE GROUP (AGE IN YEARS)	PERCENTAGE OF PATIENTS IN THIS AGE GROUP	PERCENTAGE OF MALE VS. FEMALE
2,236	65–105	95.5%	30.8% vs. 69.2%

This current study takes a theoretical approach, whereby individual patients are given consideration for the possibility of a reduction in their overall ACB by means of altering their current medication regime based on relevant practice guidelines.

Method

The scope of this study was to target a group of patients who can be identified as “elderly,” and possibly frail. The population studied in this project consists of residents in sheltered accommodation or in nursing facilities with varying degrees of support for activities of daily living, and all receive their medications in a DAA. A de-identified database of 2,236 such patients was analyzed. With approval from the CSU School of Biomedical Sciences Ethics Committee, these data were drawn from a community pharmacy’s DAA database, containing the profiles of medications that these patients were currently receiving, in a period of approximately four weeks. The data were extracted without identifiers by staff at Webstercare® (Leichardt, NSW) and passed to the research team as an Access™ database. Table 1 highlights some of the characteristics of the patients as given by Webstercare®.

Exclusions

There were some patients excluded from this analysis in order to preserve the quality of the final analysis and the impact of relevant individual results are not skewed or “diluted” in any way.

To be included, the patients needed to be using at least one regular medication with systemic effects. For this reason, any topical agents with little to no quantifiable systemic effects were excluded, such as lubricant eye drops, topical corticosteroids, and skin wash liquids. Following a similar logic, patients who are taking oral agents but with little to no quantifiable systemic effects, were also excluded. These included the likes of stand-alone daily, low-dose fiber supplements, simple antacids, and nutritional supplements (e.g. Two Cal®).

Identification

There are a few set criteria as to how and why agents are identified to be significant for the purposes of this study.

The Anticholinergic Cognitive Burden (ACB) scoring is based primarily on the works of two groups: Boustani *et al.* (2008) and Sittironnarit *et al.* (2011). Boustani *et al.* (2008) used a list of medications that are classified into three groups, giving each a score according to their apparent impact of anticholinergic effects on cognitive abilities. Scores are given from 1–3, with a positive correlation to the highest score with maximum impact. This forms the basis of identification of most of the agents that are included in this study. Sittironnarit *et al.* (2011) used a different and more recent list of equivalent medications using similar scales. Although the two lists are largely overlapping, they do differ in terms of the medications included and the scores assigned to them. In order to achieve an adequately comprehensive range of medications, both lists are used in this study.

In order to reduce the possibility of over-representing the extent of the impact and to achieve consistency, wherever there is discrepancy between the two groups in the scoring of individual agents, Boustani *et al.* (2008) have been given precedence and adhered to throughout the study. In order to be consistent with the logic used while compiling these lists, some agents are necessarily excluded from the study. Agents that exhibit no significant systemic actions will be excluded, even if they are obviously (and intentionally) anticholinergic in nature, such as inhaled ipratropium or tiotropium. There is no definitive evidence that these agents cross the blood–brain barrier and elicit any significant impact on the CNS and therefore cognitive function. For practical considerations, short-term medications, such as a course of antibiotics or benzodiazepines, were excluded, since this study focuses on the long-term therapeutic outcomes. Similarly, only medications that were “current” in status were included, any change in dosage and/or commercial brands was counted *once*, since no consideration of dosage-adjustment was given for the purposes of this study.

Analysis

Given the criteria mentioned above, the number of patients was then determined to be 691 ($n = 691$). Each patient’s profile was then analyzed, and the number and total score of implicated agents were identified using the ACB by Boustani *et al.*

(2008). The theoretical intervention was to attempt to identify the *likely* indication of each of these agents, and substitute an alternative for them wherever possible, as permissible by the current Australian Therapeutic Guidelines and Australian Medicines Handbooks as sources of evidence-based “best practice” standard (Neurology Expert Group, 2010; AMH, 2012). For example, if a patient was using amitriptyline (ACB = 3) with regular paracetamol and no antidepressants, then the likelihood of it being used as an adjuvant agent for neuropathic pain is high. However, the possibility of it being used as a sole antidepressant is also considered. In this case the results of substitution from amitriptyline to pregabalin (ACB = 0, for neuropathic pain) and to sertraline (ACB = 0, for depression) are identical, which represent an absolute reduction in total ACB by 3. Where there was a discrepancy in reduction between the two (or more) possible indications, the most conservative option was applied. An example of that would be promethazine (ACB = 3), which could be substituted with loratadine (ACB = 1, as an antihistamine) for a reduction of two points; or domperidone (ACB = 0, for nausea) for a reduction of three points, then the former is preferred unless there is obvious evidence to the contrary (e.g. the patient is concurrently using a different antihistamine).

Although this study is only based on theoretical intervention, it takes note of the limitations as to what changes are possible without impacting the overall therapeutic effectiveness of each patient’s individual regime. This is a *theoretical* model where the prescribers’ intentions and rationale for the use of each agent is not always clear. As such, the authors did not attempt to cease any medication based on assumptions of “not needed.” Patients who are on clozapine, for example, would be largely left unchanged. That is due to the sensitive nature of the medication both in terms of side effects and drug interactions, and the fact that they are required to be under the care of a specialist psychiatrist and subjected to regular full blood examinations (FBEs) as required by practice guidelines in Australia.

The two groups of results – the initial total ACB and the final ACB after possible reductions – were then subjected to a “Paired-Samples T-test” using SPSS[®] in order to ascertain whether or not the two groups are “significantly different,” to demonstrate a meaningful outcome.

Results

Of the 691 patients analyzed in this study, 242 of them (35%) were found to be using at least one anticholinergic agent on a regular basis at the time

of the study with significant systemic effects and thus contributing to the overall ACB. Forty-nine of these patients (20%) attracted a score of 3 or above on the ACB, which is deemed to be clinically significant (Boustani *et al.*, 2008). Figure 1 shows the constitution of patients by total ACB. Of the 35% who are using at least one agent on the ACB scale, an absolute reduction is possible in 59% of them ($n = 143$).

Further, it appears possible to reduce those from having an ACB score of 3 or above to a clinically insignificant score of 2 or less in 85% of the cases ($n = 42$). This would mean that the total percentage of patients who are potentially affected by a clinically significant anticholinergic burden could be reduced from 7.10% to 1.01%. Figure 2 shows the number of patients classified by resultant ACB scores *after* theoretical interventions.

In a Paired-Samples T-test, comparing the results of the ACB load before and after theoretical intervention, it was found that the correlation between the two sets of data (before and after the theoretical intervention) is 0.692 ($p < 0.001$). The ACB scores, however, were reduced after the intervention, and the difference is 0.331. The 95% CI (df = 690) does not contain the value of 0 (i.e. 0.272–0.391), and therefore it may be concluded that there *is* a significant difference between the two sets of data and the null hypothesis (H_0) is rejected. This can be confirmed by the fact that significance of the t-value is < 0.001 .

This study also found that of the 246,960 *counts* of items dispensed and recorded (both prescription and non-prescription) for this group of patients, 47,334 (or 19.2%) of them were of agents on the ACB scale.

Discussion

This theoretical study found that 35% of the patients are taking at least one agent contributing to ACB, 20% of whom have a clinically significant score of 3 or above; It suggests that absolute reduction of ACB is possible in 59% of the patients, and it is possible to bring 85% of those scored 3 or more to a score of 2 or less. The exceptions to the possibility of a successful intervention can include, but are not limited to, the example of clozapine mentioned in “Methods” section. Due to the well-known potential for clozapine to cause, among other things, neutropenia or even pancytopenia, rigid monitoring of full blood count (FBC) results is mandatory for any patient enrolled into the Clozapine program (Kuluris, 2007; Ronaldson *et al.*, 2011). The specific course of treatment is tailored by psychiatrists who, with expertise in their field, are also

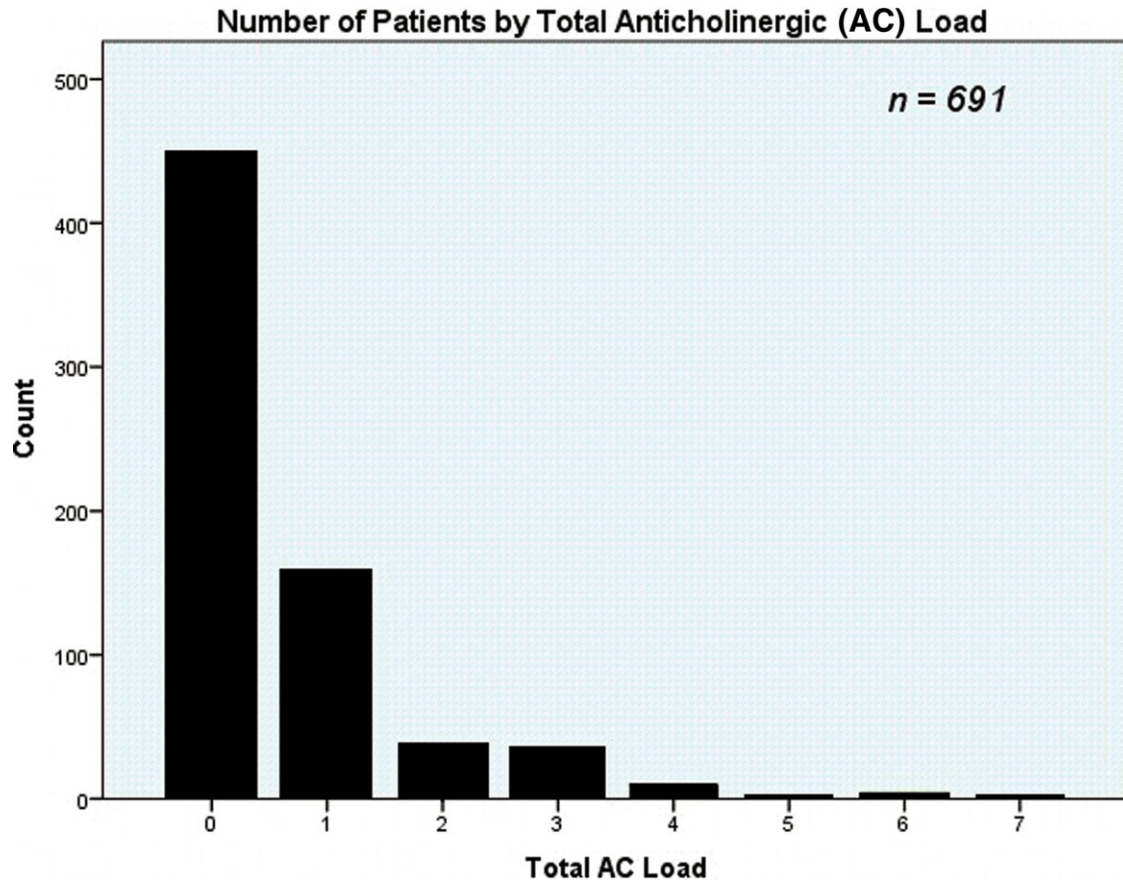


Figure 1. (Colour online) Number of patients categorized by total (individual) AC Load.

responsible for the overall therapeutic outcome of the patient. For this, and many other clinical reasons (such as drug interactions, brittle but stabilized regimens involving warfarin, phenytoin, digoxin, etc.), the physician in charge of the patient may not agree with proposed interventions from pharmacists. Therefore, at this early stage of evidence gathering, it cannot be conclusively stated that such interventions are successful or even possible. Another aspect of technical difficulties that the researchers encountered is to determine whether or not to include certain agents at various doses, since the ACB is *not* dosage-adjusted in the scope of this study. One significant example is codeine, which is recognized by a number of experts in the area to attract an ACB of at least 1. However, given that quantitative measures, such as SAA, are restricted to a laboratory setting and are not practicably available to a clinical study, it is difficult to ascertain whether or not lower dosage formulations should be included (Carnahan *et al.*, 2006). Codeine phosphate 30 mg (with or without a combination with paracetamol) should obviously be considered; however, products containing doses of 15 mg or less (typically 8 mg) are less considered. That is partic-

ularly an issue when it is only used on a *pro re nata* (PRN) basis, whereby the frequency and dosage at each dosing time is very difficult to determine from the available data. The gross inclusion of all “codeine-based” products will skew the results to reflect that more patients are afflicted with an ACB than there are in reality – even if it only attracts a clinically insignificant score of 1 on its own. In order to keep in line with the approach for consistency and inclusiveness, the researcher has decided to include them as it is listed on the two ACB scoring lists.

Lastly, the theoretical intervention conducted in this study is limited to “ideal situations.” Many practical considerations, such as Pharmaceutical Benefits Scheme (PBS) or private cost of each medicine, are crucial in the decision-making of pharmaco-therapeutic regimens. The obvious differences, such as amitriptyline (\$8.54–8.99) versus pregabalin (\$42.75–183.24) in the treatment of neuropathic pain, and oxybutynin (\$14.48) versus solifenacin (\$56.45–79.30) for urinary incontinence, are indeed as large as these are significant (MIMS Australia, 2012). Other issues such as treatment-resistance and non-compliance are taken into account in this study, but only to the extent

Final ACB Scores after Theoretical Intervention

(in patients with initial scores of 3 or greater)

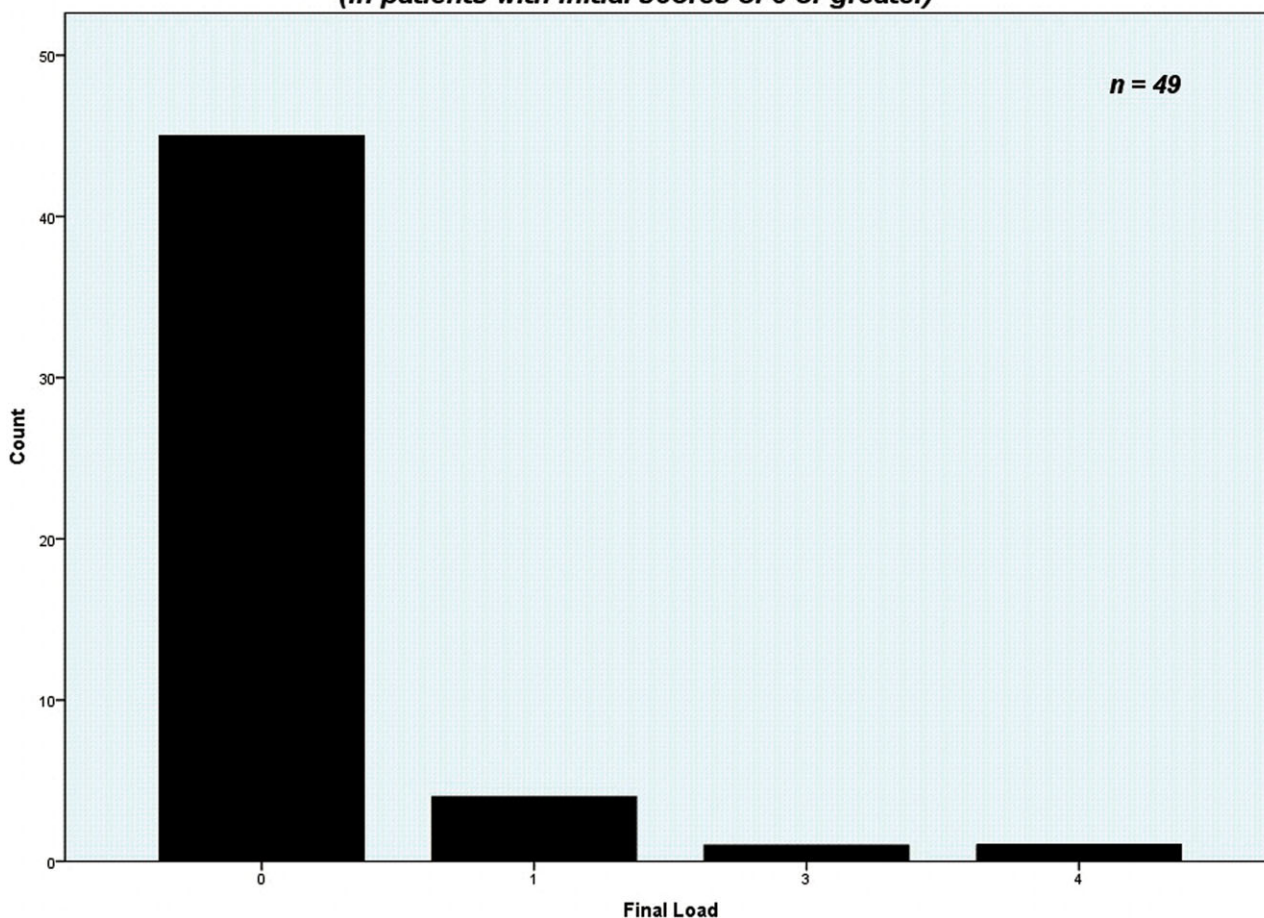


Figure 2. (Colour online) Patients grouped by final AC score for each individual studied after theoretical intervention.

of “minimizing” the impact rather than complete circumvention (e.g. lowering ACB by substituting prochlorperazine with domperidone instead of similarly effective and safe agent such as ondansetron for nausea – for cost reasons).

For these and many other possible reasons, further studies are absolutely necessary to validate, dispute, or otherwise build on these findings. The authors envision this study as a preliminary step to much larger, *actual* clinical intervention studies. At the time of writing, such intervention studies have commenced in this area. Interventions that could be suggested to the clinicians and researchers may include, for example, a protocol in which “every ACB-contributing agent intended for use is to be checked against relevant guidelines for a lower-ACB equivalent before prescribing.”

Conflict of interest

None.

Description of authors' roles

Zikai He – chief investigator, literature review, data analysis, and report writing. Prof. Patrick Ball – supervisor, contributor of data, primary reviewer of report, and project conception and design.

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