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How to manage canine cognitive dysfunction through diet, drugs and behavioural interventions

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ABSTRACT: Canine cognitive dysfunction (CCD) is a behavioural change that can occur in geriatric dogs, and is associated with impairments in learning and memory. CCD can impact the human–animal bond due to the reduction in the animal's quality of life and the owner being unable to cope with behavioural changes associated with CCD. However, early diagnosis of CCD is key in managing the condition, as its progression can be delayed with diet, medical and behavioural interventions.

Keywords: Behaviour; Drugs; Diet; Canine; Cognitive; Age

Behavioural signs of CCD

Senior animals can show a reduction in learning and memory (Osella, Re, Odore, Girardi, Badino, Barbero, & Bergamasco, 2007). Therefore, neuro-cognitive behavioural changes are generally disregarded, as this is considered to be a normal aspect of ageing. Consequently, only 12% of owners report behavioural changes to their Veterinary Surgeon (VS) despite 75% of dogs having at least one behavioural sign suggestive of canine cognitive dysfunction (CCD) (Salvin, McGreevy, Sachdev, & Valenzuela, 2010). A cross-sectional epidemiological study of older dogs found that an estimated 14.2% of dogs over eight years old had CCD, but only 1.9% were diagnosed with CCD by a VS (Salvin et al., 2010). It has been estimated that 3.4% of dogs aged 8–10 years old have CCD; however, this increases to 41% in dogs over fourteen years old (Salvin et al., 2010). Some studies, however, have found a much higher prevalence, such as Landsberg, Nichol, & Araujo (2012), who found 52% of 50 dogs over the age of nine showing signs compatible with CCD, night walking, vocalisations and anxiety being the signs most commonly displayed.

CCD is an outcome of gradual deterioration in cognitive function (Osella et al., 2007), thus affecting behaviour. Social interaction and toilet training is the most affected behaviour; however, changes in sleep–wake cycles and disorientation is also noticeably affected (Azkona et al., 2009). Typical signs also include changes in the animal's activities and interactions with their owner, other animals and their environment (Landsberg, Nichol, & Araujo, 2012). Landsberg, DePorter, and Araujo (2011) also mention senior animals might seem confused or stubborn due to compromised cognitive capabilities and short-term memory. Senior animals with CCD commonly show signs of fear, phobias, and anxiety (Landsberg et al., 2012). As there is no definitive test for CCD, the diagnosis can be challenging with other conditions associated with old age causing behavioural changes similar to CCD (Figure 1) (Landsberg et al., 2012).

Causes of CCD

The main causes of CCD is the deposition of beta amyloid protein, oxidative damage, failed repair systems and neurotransmitter dysfunction (Head, Rofina, & Zicker, 2008). Hypometabolism is also a cause of CCD, as the brain depends on the

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	Cognitive impairment	Clinical signs	Diseases that cause clinical signs similar to CCD
D	Disorientation in the immediate environment	Vocalizing, fear or phobia, hiding behaviour	Hearing loss, visual loss
I	Altered Interactions with humans and other animals	Stops jumping up during greeting, avoidance of owner, growling, aggressiveness	Arthritis, arthrosis, epilepsy, neuropathic pain
S	Sleep-wake cycle disturbances	Panting, yawning, altered quality of sleep	Renal/hepatic failure
H	House-soiling	Eliminating in new/unusual locations at home	Renal/hepatic failure
A	Changes in Activity levels & anxiety	Decreased play-time with people and other pets. Decreased interest in toys. Fear or phobia, unusual vocalizing	Hypothyroidism, hypoadrenocorticism, dilated/hypertrophic cardiomyopathy, heart blockage or valve heart disease. Behaviour diseases, painful diseases

Figure 1. Clinical signs of cognitive dysfunction and diseases that cause similar clinical signs. From: Seisdedos Benzal, A. and Galán Rodríguez, A. (2016), Recent developments in canine cognitive dysfunction syndrome. *Pet Behaviour Science*, (1), p. 50, table 1.

Drug and dose	Mechanism of action	DISHA categories improved
Selegiline[1] 0,5-1mg/kg/24h (in the morning)	Selective and irreversible inhibitor of monoamine oxidase B. Improves the levels of catecholamines in the brain cortex, promotes free radical scavenging and protects nerves from degeneration	I-S-A
Propentofylline[1] 2,5-5mg/kg/12h	Metilxantine improves blood flow to the brain, inhibiting thrombus formation and reducing peripheral vascular resistance. It enhances nutrient input to brain cells and increases the production of adenosine, a fundamental nucleoside for mitochondrial metabolism	D-A
Nicergoline[2] 0,25-0,5mg/kg/24h	Improves brain blood flow and activates cerebral metabolism. There are few studies about the effectiveness in the treatment of CCD.	A
Adrafinil[2] 20mg/kg/24h	Enhances the noradrenergic system	S-A
GABA[3] 30mg/kg/24h	Inhibitory neurotransmitter	S
Gabapentin[2] 10-30mg/kg/8-12h	Inhibition of the voltage-dependent calcium channels in the presynaptic membrane decreasing the release of excitatory neurotransmitters.	S
N-acetyl-D-mannosamine[4] 250mg/dog/24h	An isomer and a precursor of sialic acids. These are the most abundant terminal monosaccharides on glycoconjugates on eukaryotic cell surfaces and are involved in a variety of cellular functions	D-S

Figure 2. The main drugs used for canine cognitive dysfunction. From: Seisdedos Benzal, A. and Galán Rodríguez, A. (2016). Recent developments in canine cognitive dysfunction syndrome. *Pet Behaviour Science*, (1), p. 55, table 3.

availability and metabolism of glucose and oxygen resources to function correctly. Therefore, a reduction in glucose and oxygen can affect brain function and result in cognitive decline (Owen & Sunram-Lea, 2011). Beta amyloid protein is deposited within neurones at the synaptic regions of the brain (Azkona et al., 2009) and this deposition of beta amyloid protein increases with age and is connected with the severity of CCD (Head et al., 2008). Oxidative damage is caused by an accumulation of free radicals. This increases in older animals as the protective antioxidant mechanisms which removes free radicals begins to fail (Head et al., 2008). Neurotransmitter dysfunction and failed repair systems can also occur as oxidative damage to proteins, lipids and nucleotides can cause neuronal dysfunction and death (Head et al., 2008).

The plaques in the cerebral cortex and hippocampus have been correlated with CCD in dogs (Azkona et al., 2009). The location of the plaques are important, as increased plaques on the prefrontal cortex impairs reversal learning abilities (ability to modify behaviour based on experience) and plaques on the cranial aspect of the parietal lobe are associated with the behavioural changes seen in CCD (Head et al., 2008). Although Studzinski et al. (2006) state that beta amyloid can accumulate in the prefrontal cortex of dogs from eight years old, they believe signs of spatial learning and decline in memory can be seen by the age of six, suggesting the plaques are not the cause of the behavioural changes associated with CCD, but instead oxidative damage and some species of beta amyloid may be the cause, as they form before the plaques. Based on these findings, treatments that reduce oxidative damage should help to improve and prevent the deterioration of a dog's learning and memory (Head et al., 2008).

Dietary interventions

Diet modification including an antioxidant diet and nutraceutical supplements help to slow down the progression of CCD (Seisdedos Benzal & Galán Rodríguez, 2016). Halted cognitive decline, advancement in learning and improved memory is seen when dogs with CCD receive an antioxidant-enriched diet for a prolonged period of time, as antioxidants prevent oxidative damage, promote healthy brain ageing and reduce the risk of neurodegenerative disease (Head, 2009). Vitamins C and E also protect against oxidative damage to mitochondrial DNA (Heath, Barabas, & Craze, 2007) and help prevent injury to cells and their membranes and neutralise free radicals (Landsberg, 2005). Medium-chain triglycerides (MCT) are also important, as they can improve cognitive function in senior dogs by preventing hypometabolism, as it increases blood ketones. Blood ketones provide an alternative energy source for the brain, which is important as there is decreased energy metabolism in older dogs (Pan et al., 2010). Fatty acids that can be found in fish oil are required for optimal function of the brain and neural tissues. Shortages of fatty acids reduce the ability to learn and decrease exploratory behaviour (Heath et al., 2007). L-Carnitine is also important in the diet as it significantly improves brain function, memory and activity levels (Heath et al., 2007). Another important supplement is phosphatidylserine because it enhances and maintains cell activity and improves learning, memory and exploratory behaviour (Heath et al., 2007).

Many studies have been carried out to investigate different diets and supplements that can help manage CCD. To investigate the effect of an antioxidant diet, 65 beagles were split into two groups; one group received a diet with antioxidant and mitochondrial cofactor supplementation and the other group acted as controls. Dogs that were fed the modified diet made less mistakes in oddity discrimination learning tasks, and showed cognitive improvement on visual discrimination and reversal learning. Spatial memory

improvement was also noted in long-term treatment. It was also shown that the best results were seen when the diet was combined with behavioural enrichment (Head, 2009). Another study on a fortified diet containing antioxidants showed the biggest effect was seen 2 years following administration, suggesting this diet has long-term effects (Nippak, Mendelson, Muggenburg, & Milgram, 2007). In one study, 27 dogs over 8 years old took part in a trial looking at the effect of a nutritional supplement containing phosphatidylserine, L-carnitine, omega three fatty acid and antioxidants including vitamins C and E. Eleven dogs were given this nutritional supplement and 16 were given the placebo. The dogs receiving the nutritional supplement showed considerable improvement. The dogs' ability to recognise increased by half and toilet training issues improved significantly, showing a major improvement. The dogs given the nutritional supplement also slept 2 hours less during the day, thus helping improve the sleep–wake cycle (Heath et al., 2007). In another study, nine beagles over 7 years old were given a nutritional supplement containing phosphatidylserine and their short-term memory improved. The dogs performed best while on the supplement, but their performance was maintained for over 70 days after it was discontinued, suggesting this treatment has long-term benefits (Araujo et al., 2008). In another study MCT was investigated. There was a control group that received an unmodified diet and another group that received the modified diet containing 5.5% MCT. The latter group showed faster learning, improved learning ability, improved visuospatial function and was better at reversal learning (Pan et al., 2010).

Drug interventions

Medical intervention can help manage CCD symptoms by reducing anxiety and restoring normal sleep–wake cycles (Landsberg, DePorter, & Araujo, 2011). Antihistamines can improve memory, cognitive function and help with the sleep–wake cycle. However, some antihistamines have sedative effects (Parsons & Ganellin, 2006). Therefore, they should not be used if sedation and incoordination is seen during the day (Landsberg et al., 2011). Similarly, melatonin is also useful in regulating sleep patterns when given 30 minutes before sleep, but is not a sedative (Landsberg et al., 2011). The drugs adrafinil and modafinil also support normal sleep–wake cycles by increasing alertness, daytime exploration and activity (Landsberg et al., 2011). Anxiolytics can also be used in animals that find it difficult to settle (Landsberg et al., 2011), but anxiolytics can cause ataxia, disinhibit aggressive behaviour and inhibit learning and memory (Beaver, 2009), which is a considerable disadvantage. Therefore, benzodiazepines are ideal as they have short-acting anxiolytic effects and help to manage sleep–wake cycles and anxiety (Seisdedos Benzal & Galán Rodríguez, 2016). Pain is also linked with unsettled sleep, so pain management may be required and gabapentin is an ideal adjunctive therapy, as not only is it used for pain management but it also has behavioural calming effects (Landsberg et al., 2011).

Dogs with CCD may suffer from anxiety; therefore, buspirone, fluoxetine or sertraline may be beneficial as these drugs have minimal side effects and treat generalised anxiety and noise phobias (Landsberg et al., 2011). Paroxetine and tricyclic are antidepressants that can also be used to reduce anxiety, but they have some anticholinergic effects which are unfavourable; therefore, pheromones and lavender essential oil may be preferable, as these are natural compounds that can reduce anxiety (Landsberg et al., 2011).

The usual treatment choice for CCD is either propentofylline, selegiline or nicergoline (Seisdedos Benzal & Galán Rodríguez, 2016) (Figure 2). Propentofylline is used when lethargy and depressed behaviour is seen in senior dogs (Landsberg et al., 2011). Selegiline improves social interactions and sleep–wake cycles (Seisdedos Benzal & Galán Rodríguez, 2016). Selegiline is considered to be neuroprotective and may decrease nerve damage; however, clinical improvement may not be seen until six weeks post administration (Landsberg et al., 2011), which is a significant disadvantage. Selegiline should not be used alongside other monoamine oxidase inhibitors like fluoxetine and should be used carefully with drugs that enhance serotonin transmission, such as tramadol (Landsberg et al., 2011). Drug therapy alone will not address all the issues of CCD, making it important that, wherever possible, a multimodal approach to management is adopted including dietary and behavioural therapies.

Behavioural interventions

Behavioural intervention is important, as dogs with CCD are more sensitive to changes in the environment and this can impact their health and behaviour (Landsberg, Nichol, & Araujo, 2012). Having a regular, predictable routine and allowing positive interactions is important, as this can help reduce stress and anxiety (Landsberg et al., 2011). Providing non-slip surfaces such as rugs can help with orientation and also prevent falls (Landsberg et al., 2011). Adding smells, touch and sounds to the home environment can help with navigation around the home, thus maintaining familiarity and comfort. However, it is important any changes are done slowly to minimise stress (Landsberg et al., 2011). Mental stimulation is also necessary to maintain the dogs quality of life (QOL) and exercise is important to slow down CCD (Landsberg et al., 2011). In a study carried out by Cotman and Berchtold (2007), it was found that older dogs with regular access to toys, exercise and interactions with other dogs performed better in learning and memory tests compared to dogs that had no enrichment, highlighting the importance of environmental enrichment.

Behavioural intervention is imperative to reduce CCD symptoms and can help with inappropriate urination and defecation in the house. This can be attained by taking the dog out more frequently; however, it may also be necessary to put a toilet area inside the house (Seisdedos Benzal & Galán Rodríguez, 2016). It is also important to help with the dog's sleep–wake cycle to improve nighttime walking and anxiety; this can be achieved by playing or going for a walk before bedtime (Seisdedos Benzal & Galán Rodríguez, 2016). The dog should also be provided with a quiet, dark resting area and stroking the dog before bedtime can help improve sleep (Seisdedos Benzal & Galán Rodríguez, 2016).

Conclusion

Old age can cause behavioural changes similar to CCD resulting in CCD going undiagnosed. Educating owners on the signs of CCD is imperative, as early diagnosis is essential so appropriate management can be initiated, the animal's QOL can be improved and the human–animal bond can be sustained. Although CCD is not curable, it can be managed. A combined treatment of dietary, medical and environmental enrichment is required to manage CCD successfully and help to slow the rate of decline.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Multiple Choice Questions

1. According to the 'DISHA' cognitive impairment of canine cognitive dysfunction, what does D stand for?

- **(a)** Disorientation
- **(b)** Dehydration
- **(c)** Diarrhoea
- **(d)** Dysphagia

2. Which one of the following is an isomer and precursor of sialic acids?

- **(a)** Nicergoline
- **(b)** GABA
- **(c)** Gabapentin
- **(d)** N-acetyl-D-mannosamine

3. Which of the following DISHA categories is improved with the use of gabapentin?

- **(a)** Interactions
- **(b)** Sleep-wake cycle
- **(c)** House soiling
- **(d)** Activity

4. Oxidative damage is caused by an accumulation of free radicals.

- **(a)** True
- **(b)** False

5. Which of the following behavioural interventions is not recommended for dogs with canine cognitive dysfunction?

- **(a)** Increasing toileting opportunities
- **(b)** Providing non-slip surfaces
- **(c)** Providing environmental enrichment
- **(d)** Changing the environment quickly and frequently

6. How long can it take before clinical improvement can be seen after selegiline is provided for the treatment for canine cognitive dysfunction?

- **(a)** Three weeks
- **(b)** Four weeks
- **(c)** Five weeks
- **(d)** Six weeks

7. Which of the following DISHA categories is not improved by selegiline?

- **(a)** Interactions
- **(b)** Sleep-wake cycle
- **(c)** House soiling
- **(d)** Activity

8. The deposition of beta amyloid protein decreases with age and is related to the severity of canine cognitive dysfunction.

- **(a)** True
- **(b)** False

For the answers to the MCQs, please go to: **http://www.bvna.org.uk/publications/veterinary-nursing-journal**