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college of integrative veterinary therapies

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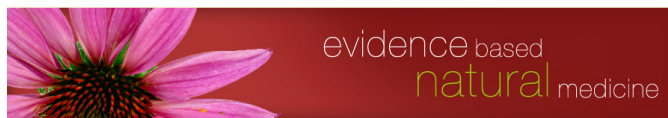
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Yucca: Treatment of Clinical Depression in a Dog with Xiao Yao San

Dr Steffi Van Der Laarse DVM CVCHM

Abstract

A female dog without physical complaints has shown depressed behavior for years. This dog responded within a few weeks to a Chinese herbal formula, Xiao Yao San, without any other modification in lifestyle or diet. The behavior has continued to improve without relapse or noticeable side effects

CASE PRESENTATION

Yucca is a Jack Russell Terrier, 9 years old. She is a sterilized female. Her bodyweight is 6 kg, her body condition is normal.

On 15 December 2010, Yucca was presented. The owner felt her dog was depressed and had been so for 8 years. Normal dog behavior is lacking. The dog shows no interest in other dogs, or humans, not even the owners. There is no display of affection towards any individual. The dog shows no interest in interaction of any kind. Yucca has been well socialized as a pup, attending puppy classes and displaying normal social interactive behavior. The problem started when, at the age of one year, the son of the owner took the dog with him on an internship. Even though she could be with him all day, her behavior started to change and she became more and more reclusive. On returning home she never fully regained her previous demeanor. The only thing Yucca is interested in is squeaky toys. Yucca avoids anybody who is obviously sad or very happy. She will not try to comfort a sad person. Anyone enticing her to play is also ignored. She never plays with other dogs. She accepts the other dog in the household, but does not seek contact with it. She gathers items in her basket: mobile phones, lighters, shoes, pens, anything she can get a hold of. There are no signs of aggression and she is timid. There is no edge to her behavior. Yucca had pups once, was a good mother but she did not seem to

enjoy it at all. She has a two year history of gastrointestinal (GI) disease, with abdominal pain, bouts of loose stools but no vomiting. There is no mucous in the loose stools, nor is it extremely smelly. She has been examined multiple times by different veterinarians, but no causative agent was identified and diarrhea resolved with aluminium hydrochloride, or without conventional treatment, only to reoccur a month later. She has been fed a commercial balanced blend of meat and vegetables for the past 18 months, previously she was on a commercial dry dog food. The change of diet has improved the GI problems but not completely resolved them. Besides this, Yucca had no health issues in the past.

Yucca had been overweight a few years ago, at 8 kg, and was on commercial dry dog food at the time. At the time of presentation she was in normal body condition. She has always been a picky eater. Blood cell counts and chemistry profiles have been done on several occasions including T4 and TSH and showed no abnormalities. There seems to be no physical cause to explain Yucca's lack of joy in life. No medication was prescribed.

Traditional Chinese Medicine Examination

Tongue is lavender and slightly swollen, consistent with Blood deficiency and Qi stagnation and/or Dampness. Pulse is very tense and narrow, normal rate. Active point is Bladder 18 with radiant heat and pressure sensitivity. Needling, with even method, Liver 3 markedly improved the pulse, making it less tense, confirming Liver Qi stagnation is the pattern here.

Traditional Chinese Medicine Diagnosis & Prescription

Qi stagnation with mild Dampness signs and Blood deficiency. The Liver is overacting on Spleen causing GI issues, manifesting as loose stools and abdominal pain. Treatment goals are to move Liver



Qi and tonify Blood, drain mild Dampness. Tonifying Liver Blood and moving Liver Qi will prevent the Liver from overacting on the Spleen causing GI symptoms. Xiao Yao San, also known as Rambling Ease Powder or Free and Easy Wanderer Powder, was prescribed at a dose of 75 mg/kg. It treats Liver Blood deficiency, Qi stagnation and drains a little Dampness if present. Xiao Yao San is an appropriate formula for both irritable bowel syndrome (IBS) and clinical depression, making it appropriate in this case due to GI issues. Xiao Yao San is a harmonizing formula: Bupleurum moves stagnant Liver Qi, Dang Gui and Bai Shao tonify Blood and Yin, Mint clears Heat, Atractylodes, Poria and Licorice support the Spleen and drain Damp.

Advice about Exercise, Diet & Additional Supplements

Yucca gets plenty of exercise, but shows no interest in other dogs or humans. The owners were advised to give her time and respect the fact that she wants to be left alone but still invite her, as much as possible, to interact with them, or other dogs. If squeaky toys are the only thing that give her joy, try to put up with the noise and let her have that joy at least.

Outcome

Within two weeks of taking the Xiao Yao San, Yucca's behavior started to change. She started to show more self-initiated movement and became more interested in what was happening around her. She started to bring toys to people in the household and invite them to play with her. She started to actively seek attention from the owners and would respond with tail wagging when spoken to. She climbed on the sofa at night and cuddled up against the owners, wanting to be caressed. Outdoors she still freezes when other dogs approach her. Her behavior has continued to improve over the last 3 months, she is a playful dog now, who wants to be caressed. This behavior, normal for most dogs, was something she had not displayed for 8 years. She is keener to go on walks, but still does not seek much interaction with other dogs.

Follow up was on 30 December 2010, 9 January 2011 and 17 February 2011. She has had no further GI issues since she started the herbal medication. Her tongue is less swollen but still a bit lavender. Her pulse is softer but still has a slightly tense feel.

Discussion on diet change

It would be expected that Yucca would improve on a fresh meat diet, since protein deficiency can give rise to decreased serotonin levels in the central nervous system which can be an important factor in depressed behavior. However, increasing the protein in her diet did not make any difference according to the owner.

Discussion on the single herbs in Xiao Yao San

Radix bupleuri - Chai Hu was found to have an anxiolytic-like effect and to reduce stress induced alteration in learning and memory behavioral tests in rats. It significantly reduced stress induced loss of cholinergic immunoreactivity in the hippocampus (Lee B, Shim I, Lee H, Hahm DH, 2009).

A combination of *Scutellaria baicalensis* and *Bupleurum scorzinerifolium* showed neuroprotective effects on iron-induced neurodegeneration in the nigrostriatal dopaminergic system of rats (Lin AM et al, 2011). The expression of glutamate and especially GABA increases in chronic pentetrazole-induced kindling in the rat hippocampus. Saikosaponins, the main active ingredients of *Radix bupleuri*, were shown to inhibit these increases and to contain glutamate and GABA expressions within normal range. There was no significant difference between the Saikosaponin group and the sodium valproate group (Xie W, Li CZ, Bao Y, Yu LJ, 2006).

Radix peoniae alba - Bai Shao. The total glycosides of Peony alleviate depression, induced by chronic unpredictable stress. The antidepressant activity is probably mediated by inhibition of monoamine oxidases and the attenuation of oxidative stress in the mouse brain (Mao QQ et al, 2009). The same author also states that neuroprotective effects could be one of the active mechanisms of antidepressants. Peoniflorin, a chief active ingredient of Bai Shao, was found to exert a neuroprotective effect on



glutamate-induced neurotoxicity in rat pheochromocytoma cells via inhibiting oxidative stress and Ca^{2+} overload (Mao QQ et al, 2010). Peoniflorin was also shown to have antinociceptive effect in rats by using bee venom. This effect was reversible with naloxone, suggesting it is mediated through endogenous opioid receptors (Yu JY et al, 2007). Peoniflorin has an analgesic effect in colorectal distension-induced visceral pain in rats with visceral hyperalgesia induced by neonatal maternal separation. The analgesic effect is possibly mediated by the adenosine A(1) receptor in the laminae I-II in the lumbosacral dorsal horn, as well as in the anterior cingulate cortex (Zhang XJ et al, 2009). Peony root was shown to have a significant antagonizing effect in scopolamine-induced memory impairment in rats. Peoniflorin, at a dose of 0.01-1 mg/kg, dose-dependently attenuated scopolamine-induced memory impairment, suggesting this may be the active ingredient responsible for the effect of peony root. Pretreatment with peoniflorin significantly prevented the scopolamine-induced decrease in acetylcholine content in the striatum, but not in the hippocampus or cortex. The decrease of acetylcholine in the striatum, cortex and hippocampus is the mechanism through which scopolamine is believed to exert its disruption of working memory (Ohta H et al, 1993).

Radix angelicae sinensis - Dang Gui contains several compounds with affinity towards serotonin receptor (5-HT₇) in a competitive binding assay. These were identified as Z-butylidenephthalide, 11(S),16(R)-dihydroxyoctadeca-9Z,17diene-12,14-diyne-1-yl acetate, (3R,8S)-falcardinol, Z-9-hepatedecene-4,6-diyne-3-one and imperatorin (Deng et al, 2006). The methanol extract of *Angelica sinensis* has been shown to exhibit competitive binding to GABA(A) receptor in an in vitro binding assay. The GABAergic ligands were identified as gelispirolide and riligustilide (Deng S et al, 2006). Japanese angelica was shown to have a significant antagonizing effect in scopolamine-induced memory impairment in rats (Ohta H et al, 1993).

Rhizoma atractylodis macrocephala - Bai Zhu contains atractylenolide I (AO-I) which was able to

inhibit LPS-induction in macrophages of TNF- α , IL-1 β and NO production in a dose-dependent manner (Wang C, He L, Wang N, Liu F, 2009). Atractenolide III (AO-III) inhibits the secretion and expression of IL-6 and release of histamine in stimulated human mast cells. Thus it could control immunological reactions by regulating cellular functions of IL-6 in mast cells (Kang TH, Han NR, Kim HM, Jeong HJ, 2011).

Poria cocos - Fu Ling inhibits phospholipase A(2), 5-lipoxygenase and elastase. Pachymic and dehydrotumulosic acids were shown to inhibit leukotriene B(4) release (Prieto JM et al, 2003). Polysaccharides in poria enhance the secretion of both immune stimulators and suppress the secretion of immune suppressors thus potentiating the immune response. The triterpenes have an inhibitory effect on phospholipase A, while triterpenoids have immune modulating activity demonstrated in immune mediated diseases like psoriasis, rheumatoid arthritis and auto-immune uveitis (Rios JL, 2011).

Radix glycyrrhizae - Gan Cao has anti-inflammatory properties due to the inhibition of nitrous oxide (NO), IL-1 β and IL-6 production in lipopolysaccharide (LPS) stimulated macrophages (Thiyayaegrajan P, Chandrasekaran CV, Deepak HB, Agarwal A, 2011).

Herba menthae - Bo He oil and (-)-menthol as its most active constituent exert their anti-emetic effect at least partly by acting on the 5-HT₃ receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site (Heimes K, Hauk F, Verspohl EJ, 2010). Methanolic extract of *Mentha piperita* has anti-oxidant, MAO-A inhibitory activity and affinity to the GABA(A)-receptor assay (López V et al, 2010).

Rhizoma zingiberis recens - Sheng Jiang has shown to inhibit expression of IL-12, TNF- α , IL1 β in LPS stimulated macrophages, it also negatively affected the antigen presenting function of macrophages. T-cell proliferation was significantly reduced in response to allostimulation with ginger extract treated macrophages as antigen presenting cells.



IFN- γ and IL-2 production by T-cells was also significantly decreased in response to allostimulation (Tripathi S, Bruch D, Kittur DS, 2008).

Discussion on serotonin metabolism

Serotonin, or 5-hydroxytryptamine (5-HT), is a biogenic amine. It has been implicated in the pathophysiology of depression, mania and anxiety disorders, IBS, emesis, migraine and pulmonary and systemic hypertension. In the central nervous system serotonin is processed in several ways. Upon neuronal depolarization, serotonin is released into the synaptic cleft. It can bind to postsynaptic receptors (5-HT receptors) or serotonin autoreceptors on the presynaptic membrane. Binding of serotonin to the autoreceptor acts as a negative feedback against further release of serotonin into the synaptic cleft. After reuptake serotonin can be recycled back into presynaptic vesicles, or broken down in the cytosol by monoamine oxidase (MAO). The major metabolite of serotonin, when broken down by monoamine oxidase, is 5-hydroxyindoleacetic acid (5HIAA).

Serotonin, originating from the enterochromaffin cells in the GI system, is released into the portal circulation and quickly eliminated from the plasma via uptake into platelets and metabolism by the liver. IBS with diarrhea has been treated with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, implying serotonin is likely to be an important player in the pathophysiology of IBS.

The earliest antidepressants, the MAO inhibitors and the tricyclic antidepressants, enhanced availability of serotonin as well as other biogenic amines, most importantly norepinephrine. The most potent and specific antidepressants are the class of drugs known as the SSRIs. They increase the amount of serotonin in the synaptic cleft and prevent the negative feedback from binding to the presynaptic receptor, thus further increasing availability of serotonin in the synaptic cleft. Depression in humans and animals is

conventionally treated with monoamine reuptake inhibitors (SSRIs) and MAO inhibitors.

The use of antidepressants in domestic animals

Clomipramine (Clomicalm®, Novartis) is registered for separation anxiety in dogs and is used off label in cats. This is a tricyclic antidepressant. The following adverse reactions have been reported: lethargy/depression, elevation in liver enzymes, vomiting, diarrhea and increased thirst (Clomicalm package insert). In humans, tricyclic antidepressants are no longer first choice medicines due to the side effects and are mostly used in treatment of refractory cases.

Fluoxetine (Reconcile®, Elanco), an SSRI, is registered for use in dogs. The indication is separation anxiety. The most common adverse reactions recorded during clinical trials with Reconcile® were calm or lethargy, reduced appetite, vomiting, shaking, diarrhea, restlessness, excessive vocalization, aggression and infrequently seizures. About 33% of dogs on Reconcile experience lethargy, calm and depression. (Reconcile package insert). This would possibly make fluoxetine of limited use in the treatment of lethargy and depression in dogs.

Discussion on Xiao Yao San as an antidepressant formula

The Chinese Medicine Depression Syndrome, called Yu Zheng, has been treated for thousands of years with herbal formulas and acupuncture. It is associated with Liver Qi stagnation, brought on by grief, sadness and excessive worry. Xiao Yao San addresses this stagnation effect and the early stages of deficiency. It is used in humans in acute and chronic cases of depression where sometimes pathology is quite severe or has been present for decades. Xiao Yao San is most appropriate in cases with introverted expressions of mental disease as it does not clear Heat which would manifest as agitation, hysteria or mania. The mechanism of action has only been partially elucidated.

A study comparing gene expression in cell cultures exposed to clomipramine, St John's Wort or Xiao



Yao San found significant up-regulation of vimentin receptors and proteins affecting energy metabolism and cytoskeleton in all three groups compared to controls. This study provides preliminary evidence for multiple common molecular targets between conventional and alternative antidepressants, which appear to collectively affect neuronal plasticity (Pennington et al, 2009).

In a placebo controlled study the effect of Xiao Yao San on postpartum depression in rats was investigated and compared to the effect of fluoxetine hydrochloride, an SSRI. Xiao Yao San treatment significantly improved the behavior indexes and levels of monoamine neurotransmitters in hippocampus ($P < 0.01$). Xiao Yao Powder and fluoxetine hydrochloride produced similar effects in rats with postpartum depression (Tao Wang et al, 2010).

Yu compared fluoxetine with a combination of Xiao Yao San and Wen Dan Tang. The results were that both treatment groups showed significant improvement on the Hamilton Depression Scale with no significant difference between groups. There were fewer adverse reactions in the Xiao Yao San/ Wen Dan Tang group than in the fluoxetine group (Yu HT 2006).

Bao et al. found that Xiao Yao San at doses of 200, 400 and 600 mg/kg significantly increased the revolutions in a forced swimming test and ameliorated brain cortex 5-HT and 5-HIAA content of restrained mice. Xiao Yao San has a significant antidepressant effect which may be related to the potentiation of brain serotonergic function. (Bao L et al, 2007).

Both tricyclic antidepressants and SSRIs are equally effective in relieving global IBS symptoms, and have some benefits in treating abdominal pain (Joong Goo Kwon et al, 2011).

Serotonin Toxicity

Caution is advocated when combining Chinese herbal formulas that have anxiolytic and antidepressant actions with pharmacological anxiolytics and antidepressants. The mechanism of these Chinese herbal formulas remains ill-defined

making interactions with pharmaceutical substances unclear and unpredictable. Serotonin toxicity has been documented in both human and veterinary medicine. Toxicities have occurred after accidental ingestion of 5-hydroxytryptophane, SSRIs, MAO inhibitors and tricyclic depressants. Concurrent opioid use increases the risk of serotonin toxicity. Tramadol especially is a concern since phenylpiperidine-opioids, tramadol and dextromethorphan are all weak SSRIs, but tramadol may also act as a serotonin releaser (Mohammad-Zadeh L.F, Moses L, Gwaltney-Brant S.M, 2008).

Conclusion

Xiao Yao San provides an alternative treatment for depression in dogs with the appropriate Chinese medical diagnosis. ■

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