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Risk management of nutritional supplements in chronic illness: the implications for the care of cancer and depression

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The use of complementary medicines in patients suffering from chronic illnesses such as cancer and depression is widely documented. Current studies suggest that the prevalence of the use of complementary medicines in patients with cancer ranges from 7% to 80%. In patients suffering from severe depression the use of complementary medicines may be >40%. The aim of the present review is to systematically explore the main dimensions that clinicians have to consider when advising patients suffering from these conditions. The Medline and Cochrane databases were searched for evidence relating to the benefits and risks of supplements in the treatment of cancer and depression, including the potential interactions with pharmaco- and radiotherapy. Supplements predominantly used by patients with cancer include vitamins A, C and E, β-carotene and ubiquinone 10. Supplements predominantly used by patients with depression include S-adenosylmethionine, L-tryptophan and 5-hydroxytryptophan and inositol. Supplements potentially used by both groups include *n*-3 fatty acids, Se and folic acid. Four dimensions are identified and discussed: effectiveness; safety; communication; medico-legal aspects. These dimensions have to be addressed in an illness- and case-specific context. This task can be complex given the emerging clinical evidence, patients' own preferences and expectations and current prescribing guidelines.

Nutritional supplements: Risk management: Cancer: Depression

The use of complementary medicines in patients suffering from chronic illnesses is widely documented[1–4]. In the present paper the implications of supplement use are explored for cancer and depression. Current studies suggest that the prevalence of the use of complementary medicines in patients with cancer ranges from 7% to 80%[2,5]. For depression the prevalence may also be high, >40% in patients with severe depression[6]. Both cancer and depression are conditions that, although fundamentally different, share some common features. They may also co-exist. The clinical course can be variable, with complete remission at one end of the spectrum or death at the other. Both conditions are often chronic and may involve a succession of several recurrences and remissions. Patients may not fully recover between episodes and may continue to suffer adverse effects from their treatments. Consequently, it is not surprising that feelings of helplessness and hopelessness are common. Some patients develop 'guilt' feelings, including the feeling of having brought their condition upon themselves or deserving to be punished. Patients may feel that their physical and mental integrity is fundamentally threatened. This state of mind can lead to a sense of powerlessness, loss of control and anxiety[7,8].

Taking complementary alternative medicines and supplements may be, for many patients, a way to regain some control over their illness and ownership of their treatment. Clinicians need to be aware of their patients' motivations and anxieties when discussing the potential benefits and risks of supplements. This task can be complex because the evidence base, albeit expanding, remains limited for many supplements.

The aim of the present review is to systematically review the main dimensions that clinicians must consider when advising patients on supplement use. These dimensions are explored using cancer and depression as examples of common chronic illnesses.

Methods

Supplements likely to be used in cancer or depression were reviewed with reference to effectiveness and safety. The

Abbreviation: SAMe, S-adenosylmethionine.
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Table 1. Supplements commonly used for cancer prevention and treatment

Supplement	Effectiveness based on trial evidence	Potentially-serious side effects	Potentially-significant drug interactions
Se	Potentially effective for the prevention of gastrointestinal cancers[73] Clinical trials for prostate cancer ongoing (SELECT Trial)[12]	Potential slight ↑ in squamous and non-melanoma skin cancer risk at a dose of 200 μg daily[81] Acute toxicity: nausea causes vomiting, nail changes, irritability and weight loss; chronic toxicity resembles As toxicity[82]	Chemotherapy Modification of chemotherapies relying on oxidative stress including taxols, anthracycline antibiotics, 5-fluorouracil, Pt agents, irinotecan[89–91] Unclear whether Se only reduces toxicity and improves therapeutic index of the respective chemotherapies or may affect long-term prognosis by reducing chemotherapy effectiveness[11] May ↑ cetuximab efficacy in metastatic colorectal cancer[92] Other Potential ↓ effect of statins, ↑ effect of anticoagulants including warfarin[82] May exacerbate hypothyroidism in patients with I-deficient hypothyroidism[93]
Vitamin A	Resolution of oral leukoplakia[74] No effect on the prevention of gastrointestinal cancers[73]	↑ Mortality, statistically significant[43] Acute toxicity leads to neuro-psychiatric symptoms including delirium and coma[83] Hepatotoxicity[84,85] Hypervitaminosis leads to skin, bone and nail abnormalities[86] Benign intracranial hypertension[87,88] ↓ Bone density and ↑ risk of hip fracture with long-term dietary intake[45]	Other hepatotoxic drugs, including alcohol: ↑ liver toxicity[85] Retinoids: ↑ overall toxicity[83] Tetracyclines: ↑ benign intracranial hypertension[87] Warfarin: ↑ in bleeding risk through vitamin K antagonism[83]
Vitamin C	Possibly no benefit for prevention and treatment[75] No effect on the prevention of gastrointestinal cancers[73] Potential ↓ in breast-cancer risk[76]	Effect on mortality unclear[43] Potential kidney damage through oxalate formation[86] Rebound scurvy after high doses of ingestion[86]	Chemotherapy High dose leading to nephrotoxicity through accumulation of methotrexate and precipitating metabolites[46] Other Statins: ↓ effectiveness in combination with other oxidants[94] Oestrogen: ↑ in plasma levels in patients with low baseline concentrations of vitamin C[94]
Vitamin E	Possibly no benefit for prevention and treatment[75] No effect on the prevention of gastrointestinal cancers[73] ↓ Risk of prostate cancer incidence and mortality in male smokers[77] No effect on the incidence of and mortality from upper aerodigestive tract cancers[78]	↑ Mortality[43] Higher mortality from haemorrhagic stroke in male smokers[14]. Risk later confirmed only for hypertensive smokers[60]	Chemotherapy ↓ in cisplatin-induced neurotoxicity[95] Other Cyclosporin: water-soluble forms of vitamin E may ↑ absorption[96] Statins: ↓ effectiveness in combination with other oxidants[97] Anticoagulants and anti-platelet drugs: high dose vitamin E antagonises vitamin K-dependent clotting factors[97]
β-Carotene	Resolution of oral leukoplakia[74] No effect on the incidence of and mortality from upper aerodigestive tract cancers, although potential ↓ in incidence of some laryngeal tumours[78] No effect on the prevention of gastrointestinal cancers[73] Potential ↓ in breast cancer risk[76] Clinical trials for prostate cancer ongoing (SELECT Trial)[79]	↑ Mortality[43] ↑ Mortality from lung cancer and IHD in male smokers[14] ↑ Incidence of lung cancer, ↑ mortality from lung cancer and CVD in smokers, ex-smokers and asbestos workers[50] Excess risk not apparent after 4–6 years (non-randomised follow-up)[13] ↑ Risk of prostate cancer incidence and mortality in male smokers[77]	Statins: ↓ effectiveness in combination with other oxidants[98]

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Table 1. Continued

Supplement	Effectiveness based on trial evidence	Potentially-serious side effects	Potentially-significant drug interactions
Ubiquinone 10	Preliminary but inconclusive evidence of protection against cardiotoxicity or liver toxicity during cancer treatment[80]	Hypotension	Warfarin: ↓ efficacy[99] Antihypertensives: ↑ effect[99]

↑, Increase; ↓, decrease.

Medline and Cochrane databases were searched for evidence relating to the benefits and risks of supplements in the treatment of cancer and depression, including the potential interactions with pharmaco- and radiotherapy. Search terms included the identified supplements and vitamins. Additionally, the keywords 'antioxidants', 'CYP', 'toxicity', 'high dose', 'recommended daily intake', 'serotonin', 'serotonin symptom', 'benefit', 'effect', 'effectiveness', 'risk', 'mortality' and 'mechanism of action' were searched. The recovered papers were reviewed for further relevant references. In order to identify potentially-serious side effects and drug interactions web-based resources such as the Natural Medicines Database 2007[9] were used. Where available, systematic reviews, meta-analyses and randomised controlled trials were given priority. The results were then interpreted in relation to their potential implications for the clinician–patient relationship and medico-legal issues.

Results

Four dimensions are identified and discussed: effectiveness, safety, communication and medico-legal aspects. These dimensions have to be addressed in an illness- and case-specific context.

The effectiveness dimension

Supplements predominantly used by patients with cancer include Se, vitamins A, C and E, β-carotene and ubiquinone10. Supplements predominantly used by patients with depression include S-adenosylmethionine (SAMe), L-tryptophan and 5-hydroxytryptophan, folic acid, *n*-3 fatty acids and inositol. The choice of supplements in cancer and depression is mainly but not exclusively guided by identified pathophysiological pathways.

Supplements commonly used for cancer prevention and treatment. Patients with cancer commonly use antioxidants to protect the body against O_2-induced tissue damage by handling free radicals and H_2O_2. Oxidative stress occurs as part of the normal metabolism, but is also exploited as a chemotherapeutic target in, for example, treatment with anthracycline antibiotics and radiotherapy[10]. Oxidative stress may also contribute to undesirable severe side effects such as doxorubicin-induced cardiotoxicity[10,11]. The effectiveness of antioxidants may depend on their ability universally to either prevent tissue damage or specifically to repair damage where it has occurred. It seems intuitive to assume that repairing existing tissue damage may be the harder task, requiring higher supplement doses. Also, it may be necessary to match the antioxidant properties to the oxidative mechanism that led to the particular tissue damage originally. The choice of antioxidant as well as the specific formulation of the chosen antioxidant may be important[12]. This factor may explain why the effectiveness of most antioxidants in cancer prevention has been rather limited (Table 1). Currently, Se seems to be the most promising supplement, but doubts have been raised about whether the observed anticarcinogenic effects are associated with its pro-oxidant properties rather than its antioxidant properties. Some forms of Se are able to form reactive oxygen species that may induce apoptosis[12]. For instance, Na_2SeO_4 may be a more potent reactive oxygen species donor than organic forms of Se such as selenomethionine, which seems to be more commonly used. Trials are required to compare the efficacy of both forms[12]. The concept that antioxidants can develop pro-oxidant properties under specific conditions may also potentially explain why β-carotene in combination with smoking may actually increase the mortality from lung cancer[13,14].

Supplements commonly used for depression. Supplements used in the treatment of depression include *n*-3 fatty acids, SAMe, 5-hydroxytryptophan, L-tryptophan, folic acid and Se (Table 2). As with many conventional antidepressants, the objective of using SAMe, 5-hydroxytryptophan, L-tryptophan and folic acid is to increase serotonin availability and/or activity. SAMe, *n*-3 fatty acids and inositol seem to influence cell-membrane composition and second-messenger systems, thereby modifying synaptic neurotransmission.

L-Tryptophan is an essential amino acid that is absorbed from dietary proteins, converted to 5-hydroxytryptophan and then to 5-hydroxytryptamine, i.e. serotonin. In contrast to peripheral serotonin, both L-tryptophan and 5-hydroxytryptophan can cross the blood–brain barrier. However, only 10% of L-tryptophan is available to the serotonin pathway, whilst the rest is metabolised by an alternative pathway, so that 5-hydroxytryptophan may be more effective at increasing serotonin synthesis[15]. Clinical evidence is sparse, presumably because of the continued concerns about an association with eosinophilic myalgic syndrome (see p. 488). The available trial evidence suggests that both L-tryptophan and 5-hydroxytryptophan may be effective antidepressants[16].

SAMe is produced from methionine and ATP. Folic acid is a cofactor in the methylation of homocysteine to methionine[17,18] and may exert its antidepressant action through the increase in SAMe. However, the exact mechanism of the antidepressant action is not clear. SAMe is a methyl donor required for the synthesis of many

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Table 2. Supplements commonly used for the treatment of depression

Supplement	Effectiveness based on trial evidence	Potentially-serious side effects	Significant drug interactions
n-3 Fatty acids	EPA or a combination of EPA and DHA are effective as adjunctive treatment. EPA may have a maximally-effective dose of 1 mg/d[25] ↑ Remission period when added to Li in bipolar effective disorder[57]	Contamination possible, e.g. with organic pesticides or Hg[47,100]	Vitamin A: ↑ risk of toxicity[101]
SAMe	Parenteral SAMe superior to placebo[21] Comparable efficacy to imipramine in two RCT[22], oral SAMe requires high dose (1600 mg)[22]	Induction of mania in patients with bipolar affective disorder[64,65]	All drugs with direct or indirect serotonergic effects including antidepressants and opiates[66]
L-Tryptophan, 5-hydroxy-tryptophan	Preliminary trial evidence of benefit[16]	Eosinophilic myalgic syndrome: aetiology and contaminants remain unresolved[48] Theoretically, mania is possible	All drugs with direct or indirect serotonergic effects including antidepressants and opiates[66]
Folic acid	Effective as adjunctive treatment and potentially also as monotherapy. Effect may be dose dependent[23]	Potential stimulation of bone marrow[52] ↑ Risk of cancer-cell stimulation in dose higher than RDA[53]	Theoretically, partial reversal of anti-folate therapy, e.g. Methotrexate[56]
Inositol	Evidence inconsistent[29]. No significant effect as augmentation treatment for treatment resistant bipolar depression[31,32]	Theoretically, mania is possible[28] Fast relapse once treatment discontinued[102]	None reported Theoretically may ↓ efficacy of Li in spite of its own potentially mood-stabilising and antidepressant function[27]

↑, Increase; ↓, decrease; SAMe, S-adenosylmethionine; RCT, randomised controlled trial.

neurotransmitters. SAMe increases serotonin activity in human subjects and has also been shown to increase cerebral concentrations of serotonin and noradrenaline in animal experiments[17]. Methylation is also involved in maintaining the integrity of cell membranes, rendering them more fluid. This process may change the configuration of membrane-bound receptors and ion-channels and alter neurotransmission patterns. G protein–receptor coupling–uncoupling dysfunction, which has been implicated in the genesis of mood disorders, may be counteracted[17,19]. Interestingly, stabilisation of neuronal membranes and modulation of second messengers are also purported mechanisms of action for mood stabilisers such as Li and valproate[20]. SAMe has been shown to be superior to placebo and equivalent to tricyclic antidepressants[21,22] and folic acid[23] as an adjunctive treatment for depression.

EPA and DHA are two *n*-3 fatty acids that are integral components of neuronal membranes such as synaptic, dendritic, mitochondrial and vesicle membranes[24]. Thus, if there is a lack of these fatty acids the integrity of neuronal membranes and the corresponding neurotransmitter activity may be disturbed. EPA and DHA may have several mechanisms of action operating at different levels. They seem to exert their effectiveness through modification of the cell-membrane structures and influence serotonergic and dopaminergic neurotransmission, regulate corticotrophin-releasing factor and suppress phosphatidylinositol second-messenger activity[25]. Additionally, *n*-3 fatty acids have blood-thinning effects that may improve cerebral perfusion[25]. Current evidence suggests that EPA alone or in combination with DHA is effective as adjunctive treatment for depressive episodes, in the context of either a unipolar depression or a bipolar disorder[25].

Inositol is yet another substance that has a mechanism of action that is linked to cell-membrane composition. Inositol is a component of cell-membrane phospholipids and a constituent of the intracellular phosphatidylinositol second-messenger system that is linked to serotonin, noradrenaline and cholinergic receptors[26]. Disturbance of this second-messenger system has been implicated in the genesis of depression[27,28]. It has been suggested that decreased phosphoinosite signalling may lead to depression, whereas increased signalling may lead to mania[29]. The clinical evidence supporting the use of inositol, however, remains limited[30–32].

Se has also been implicated in the treatment of depression, but no trial has been conducted. Its antioxidant qualities may reduce nerve-cell damage. Additionally, Se is an important cofactor in the conversion of thyroxin to liothyronine. Notably, the brain receives a priority supply in the presence of Se-deprived states[33]. In animal experiments increased dopamine and serotonin turnover has been shown to be associated with low Se intake[34]. Also, mood states seem to correlate with Se plasma levels[35,36]. Whether Se supplementation is an effective treatment of depression remains unclear; a recent trial in healthy volunteers has not found any improvement of mood[37].

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Table 3. Safety margins for selected supplements

Supplement	Safe upper level (mg)[45]	↑ Risk of significant side effect[45]	Estimated mean daily consumption (mg)[45]	Dose range reported in studies[43] mg	IU	Other*	Range of tablets needed for potentially unsafe use according to supplement strength (*n*)
Se	0·45		0·039	0·025–0·20			2–20
β-Carotene	7		2·3	1·2–50			<1–4
Vitamin A		>7500 µg RE for chronic toxicity	520 µg RE		1333–200 000	400–60 000 µg RE	<1–17
		3000 µg RE for teratogenecity					<1–6
		>1500 µg for ↑ risk of hip fracture					<1–3
Vitamin C		>1000 for certain groups†	64	80–2000			2–11
		>3000 or 4000 for ↑ risk of gastrointestinal problems					2–37 or 50
Vitamin E	537		8·5	6·71–3350	10–5000		>1–117

↑, Increase; RE, retinol equivalent.
*Substance equivalents.
†Heterozygous for haemochromatosis and thalassaemia or predisposition to urinary or renal stones.

The safety dimension

Taking supplements is not without potential risks. Complementary and alternative medicines have, rightly or wrongly, a very positive 'natural' reputation among substantial sections of the population, and therefore can be popular with patients from a wide variety of cultural backgrounds[4]. The potential health risks depend on whether treatments are taken alternatively to or complementary with conventional treatments. If supplements are taken as an alternative treatment there is a risk that patients abandon conventional treatments, potentially to their detriment.

If supplements are taken complementary with conventional treatments health risks may arise from potentially-serious side effects or drug interaction with conventional medicines. Some health risks may arise from either source. Some of these potential health risks are more tangible than others and therefore may be difficult to quantify. Equally, it can be difficult to predict how research results based on large studies measuring general outcomes such as 'all-cause mortality' will impact on individual cases. In particular, the discrepancy between the research findings from large epidemiological studies and randomised controlled trials and meta-analyses needs to be explored further. Although large-cohort studies seem to suggest that antioxidants are generally beneficial[38–42], the outcomes from a recent meta-analysis[43] seem to suggest otherwise. This meta-analysis of sixty-eight randomised controlled trials has found that treatment with β-carotene, vitamin A and vitamin E increases all-cause mortality (Tables 1 and 2).

Some potential health risks can be derived from the purported mechanism of action. Again, it may difficult to predict how such theoretically-derived risks translate into clinical evidence. Obviously, it is unlikely that such risks will be quantified in future, since it would be unethical to initiate studies that purport to explore a potential harmful event as the principal outcome.

Toxic effects. The therapeutic index of a supplement, i.e. the relationship between therapeutic dose and toxic dose, depends on many individual factors, including supplement formulation, water solubility, organ function and other medications taken concomitantly. This margin of safety may be particularly problematic if patients take supplements at higher than the recommended dose[44]. For instance, Se has a narrow therapeutic index. The upper level of safety as recommended by the UK Food Standards Agency[45] is 0·45 mg total Se/d. Se supplements are usually used in strengths between 0·025 and 0·2 mg daily, leaving a narrow margin for patients who chose to take a higher than recommended dose. Calculations can be confusing for those supplements measured in more than one unit, e.g. IU, milligrams or substance equivalents. For some supplements, such as vitamin A, the Food Standards Agency has not issued a safe upper level; thus, defined adverse events such as increased risk of hip fracture and teratogenecity are used as surrogate indicators (Table 3). Usually supplements are offered in various preparations, combinations and in a wide dose range, e.g. for vitamin A from 400 µg retinol equivalents to 60 000 µg retinol equivalents (1333–200 000 IU). Furthermore, patients may combine different preparations without realising the

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Table 4. Potential thoughts and associated mood about complementary and conventional medicines

Thought	Potential mood	
	Thought accepted by others	Thought not accepted by others
Complementary medicines are natural and thus harmless. They have less side effects	Safe	Insecure, anxious, suspicious
Complementary medicines are more effective than conventional therapies	Excited	Defensive, ridiculed
Conventional therapies have poisoned me	Aggrieved, angry	Angry, deceived
Conventional therapies have not worked for me	Disappointed, frustrated	Angry, patronised
Complementary medicines boost the effect of my treatment	Hopeful	Rejected, hopeless, helpless
Complementary medicines restore my balance with nature	Hopeful, guilty	Hopeless, guilty
Complementary medicines give me control and ownership of my treatment	Assertive	Humiliated, patronised

potential of accumulation and associated risks when exceeding safety margins. It may be necessary to highlight to patients how many tablets of a chosen supplement are likely to lead to adverse events (Table 3).

A particular problem arises when high-dose vitamin C is combined with methotrexate (a chemotherapy drug). This combination may increase methotrexate toxicity and could lead to kidney damage as result of increased plasma methotrexate levels and thus methotrexate toxicity. Vitamin C acidifies urine and leads to the precipitation of methotrexate and its less-water-soluble metabolites[46].

Contamination. Supplement contamination can also lead to potential health hazards. Fish oil containing *n*-3 fatty acids and 5-hydroxytryptophan are commonly cited examples. Some cod-liver-oil products have been reported to be contaminated with toxins and pesticides such as polychlorinated biphenyls, hexachlorobenzene, hexachlorocyclohexane isomers and chlorinated pesticides (dichlorodiphenyltrichloroethanes)[47]. Even if acceptable safety levels are not exceeded, these substances may accumulate over time. Contamination with heavy metals, in particular Hg, may be a further concern if fish oils are produced from fish caught in contaminated waters. Nevertheless, the overall benefits of *n*-3 fatty acid supplementation are judged to exceed the potential risks[47].

L-Tryptophan and, to a lesser extent, 5-hydroxytryptophan have been associated with eosinophilic myalgic syndrome. In 1989 1500 cases of L-tryptophan-associated eosinophilic myalgic syndrome were reported, most of which could be traced back to one single manufacturer. The incidence dropped dramatically after L-tryptophan products were limited[48]. However, the association has not been fully clarified and five potential contaminants have been identified[49].

Carcinogenesis. The finding that β-carotene, traditionally used as an antioxidant, was associated with an increased incidence of and mortality from lung cancer in smokers, ex-smokers and asbestos workers[14,50] was unexpected. The mechanism of this adverse effect remains unclear, but may be related to either the pro-oxidative properties of some β-carotene cleavage products or a direct mutagenic effect[51].

Folic acid is a basic component of cell metabolism and DNA synthesis and repair. Rapidly-dividing cancer cells have an increased requirement for folate to maintain DNA synthesis[52]. Thus, supplementation with folic acid, possibly from a dose of folic acid of 800 µg/d, may potentially induce tumour-cell proliferation[53].

Obviously, any supplement contaminated with a carcinogenic substance such as some fertilizers and heavy metals may promote cancer, and patients should be advised to acquire their supplements from a reliable source at all times.

Potential reversal of efficacy of chemotherapies. Chemotherapeutic agents relying on oxidative stress include alkylating agents (e.g. cyclophosphamide, anthracycline) antibiotics (e.g. doxorubicin) and epipodophyllotoxins (e.g. etoposide). Essentially, these agents produce reactive oxygen species to target DNA, thereby arresting cell cycles and inducing apoptosis. Antioxidants may suppress free radical formation and thus compromise the ability of chemotherapeutic agents to destroy micrometastases. This outcome could translate into higher risk of recurrence[10,11]. Antioxidants may also promote multi-drug resistance mediated through membrane transporter proteins. Equally, radiotherapy depends on irradiation-induced free radical formation. As a result, antioxidants may at least theoretically compromise radiotherapy results[54,55].

Folic acid, because of its crucial role in DNA metabolism, is an obvious therapeutic target for anti-tumour agents. Theoretically, folic acid supplementation may decrease the efficacy of anti-folate chemotherapies. However, folic acid may also reduce the likelihood of anti-folate-associated serious adverse effects[56]. As long as the evidence remains conflicting caution is required.

Anticoagulation leading to serious bleeding. *n*-3 Fatty acids have been shown to inhibit platelet function. Thus, the logical question is whether *n*-3 fatty acids could carry a serious bleeding risk. The available clinical evidence has not upheld such concerns, even for combinations with anticoagulants such as warfarin or aspirin[57,58]. Thus, *n*-3 fatty acids are rated as generally safe. Even if the risk is low, however, it does not mean that severe bleeding events can ever be excluded in individual patients. Recently, a case of subdural haematoma in an elderly patient taking high-dose *n*-3 fatty acids in combination with warfarin and aspirin was reported[59].

Vitamin E may antagonise vitamin K-dependent clotting factors, which could translate into an increased risk of haemorrhagic stroke[60]. Such an increased risk was reported for male smokers in the original

Alpha-Tocopherol, Beta-Carotene Prevention Study[14], although subsequently the risk has only been confirmed in the presence of hypertension[60]. A 6-year follow-up study has found that the risk of cerebral infarction is increased by 13%, but the investigators suggest that this finding could be a result of chance because no other trial has highlighted an association between vitamin E and stroke[61].

Serotonin syndrome and induction of mania. Serotonin syndrome is caused by an excess of serotonin in the brain. It is rare but can be potentially life-threatening in its severe form; the extent of severity seems to be dose related. The features of severe serotonin syndrome include autonomic instability, hyperthermia, agitation, hyperreflexia and seizures. Serotonin syndrome can occur when serotonergic drugs or supplements are combined with each other or with substances that facilitate a serotonergic response such as opiates and Li[62]. All serotonergic supplements reviewed here can increase the risk of serotonin syndrome, and a case of serotonin syndrome after the ingestion of tryptophan, St John's wort (*Hypericum perforatum*) and another unknown substance has been reported[63]. All serotonergic supplements may increase the risk of manic episodes in predisposed patients through increased serotonergic neurotransmission, either on their own or more likely in combination with other serotonergic drugs[64–69].

The communication dimension

In order to understand why patients with cancer and depression may take complementary medicines and specifically supplements it is worthwhile to explore some of the cognitions such patients may experience. As could be expected, the associated mood states can be powerful (Table 4), and it can easily be seen that criticism delivered insensitively can lead to a breakdown of the therapeutic relationship. If the relationship is breaking down, it may be useful to recall this cognitive mindset and the associated emotions. Clinicians must remember that patients make a great emotional investment when trying to take the initiative to re-gain autonomy over a state that may often be perceived as out of control and hopeless. Thus, it is important that patients feel that their views are accepted, even if they cannot be endorsed. At all times it is important to work towards a collaborative relationship.

The medico-legal dimension

In a time when it has become increasingly difficult to distinguish between defensive medicine and defensible medicine, advising patients on supplement use may cause a dilemma. Clinicians need to be aware of supplement-induced side effects or interactions and should be able to identify hazards, advising patients accordingly and avoiding uncritical encouragement of potentially-harmful use. Ignorance in this area, given the independent usage of complementary and alternative medicines, may lead to criticism and possibly litigation[70]. As a starting point, clinicians should always ask about supplement and over-the-counter drug use when taking a history. However, overcautious warnings about the danger of everyday foodstuffs may be equally counter-productive and convey the impression that the clinician is out of touch with reality. Ultimately, Paracelsus' view that 'all things are poison and nothing is without poison, only the dose permits something not to be poisonous'[71] still holds today.

When discussing supplements clinicians must also consider whether there is a sufficient evidence base for their use at all. Clinicians must further consider which risks would ensue if patients took supplements instead of indicated conventional medicines. This approach is also reflected in UK General Medical Council guidelines on 'Good practice for prescribing medicines'[72]. In addition to adhering to all general principles of prescribing the clinician must:

- be satisfied that an alternative licensed medicine would not meet the patient's needs;
- be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy;
- take responsibility for prescribing the unlicensed medicine and for overseeing the patient's care, including monitoring and any follow up;
- record the medicine prescribed and, where the clinician is not following common practice, the reasons for choosing this medicine in the patient's notes.

Conclusions

Advising patients on the risks and benefits of supplements is a multidimensional task, which must be guided not only by the available clinical and theoretical evidence but also by psychological and medico-legal considerations. For many but not all supplements the clinical evidence for effectiveness and safety remains inconclusive. Nutritional benefits may not translate into benefits from complementary supplement use, and correction of a supplement deficiency may not necessarily lead to the resolution of targeted symptoms. Meta-analyses can be misleading if the studies entered are small and of poor quality and publication bias is not discussed. Equally, it is difficult to monitor the safety of over-the-counter drugs. Ultimately, in many cases patients will have to find their own trade-off between expected benefits and potential risks. Preferences and expectations have to be explored and responded to in the light of the emerging clinical evidence in this area. Decision analyses that formally investigate patients' preferences when trading-off different alternatives are required to gain a deeper understanding of the likely drivers for individual decisions.

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