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Opinion

Studies of Mechanisms Involved in Successful Embryo Implantation Has Led to Novel Highly Effective Treatments for a Plethora of Chronic Illnesses and Advanced Cancer

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Introduction

There are similarities between the fetal-placental unit and malignant tumors including rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance. One of the important steps for a successful pregnancy is to develop some uterine arteries with thin cell walls, during the secretory phase of the menstrual cycle in contrast to the arteries with thick walls during the proliferative phase. There is evidence that at least some of the thin-walled spiral arteries created during the secretory phase are derived from the re-modeling of the thick-walled uterine arteries by an autoimmune mechanism [1-3]. Though there are many downstream molecular pathways that are needed to increase cellular immunity to remove the thick walls, there has been evidence to suggest that the initiation of the cascade may be related to progesterone (P) blocking the effect or the release of dopamine. This biogenic amine functions to diminish cellular permeability. Thus, there exists the possibility that the normal increase in inflammatory white blood cells required for the uterine artery remodeling is initiated by infiltration of irritants into the pelvic tissues [4]. The possibility thus exists that excess infiltration of irritants may cause a greater degree of inflammation than required for normal remodeling leading to infertility related to excessive endometrial inflammation, usually, but not necessarily, associated with pelvic pain [5].

We had noticed that many women treated with dopaminergic drugs not only improved aspects of pelvic pain but, also other symptoms and conditions including headaches, interstitial cystitis, Crohn's disease, ulcerative colitis, and even severe constipation [6-10]. Thus, it made sense that increased cellular permeability could be the etiologic factor in many different conditions, and that they could respond also to dopaminergic drugs, e.g., dextroamphetamine sulfate, which we mostly used, and the use of cabergoline.

Opinion

Though we had many cases of various treatment refractory conditions that dramatically improved following treatment with dextroamphetamine while treating pelvic pain beginning about 45 years ago, we did not write our first case report until 1984 in a woman who had severe urticaria almost daily covering most of her body, who within one month got total remission of urticaria which has persisted now for 50 years (but resumes if she temporarily stops it usually due to a shortage) [11]. Actually, we did not publish our first case related to a type of pelvic pain, i.e., interstitial cystitis, until 2005 and pelvic pain in 2007 though we had hundreds of women improving before these publications [12,13].

The delay in our publishing case reports of improvement re-

garding the amelioration of multiple medical conditions was related to my indoctrination that the publications with the most scientific merit are Randomized Controlled Trials (RCTs), or at least large series. There were so many women with pelvic pain who improved with dopaminergic drugs, but we failed in our endeavor to convince the manufacturer to support an RCT. The best we could do was perform a 50-patient prospective study of dopaminergic drugs for chronic fatigue syndrome (with very good results) and weight gain despite dieting related to orthostatic edema [14,15]. We do refer to a series performed by one of our colleagues who tried it after hearing one of our lectures (Paul Carpentier) who presented his data concerning pelvic pain at the American Society for Reproductive Medicine, and we published his data in one of our reviews [4].

Over the years we realized that so many RCTs reach one conclusion only to be refuted by another RCT, so it leaves the clinician confused as to what to believe and how to treat. Thus, we became more convinced about publishing very convincing case reports. Similarly, very convincing case reports were published concerning the use of dextroamphetamine (mostly) and cabergoline (minority) that have been summarized in 2 reviews [16,17]. References to these case reports are provided in these 2 reviews [16, 17]. These cases have included all types of pelvic pain, mittelschmerz, dyspareunia, vaginismus, vulvovaginitis, interstitial cystitis, headaches of various etiologies, recurrent aphthous stomatitis, burning mouth syndrome (stomatodynia), chronic sinusitis, chronic thyroiditis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, microcytic colitis, gastrocolic reflux, Meniere's disease, autoimmune hearing loss, angioedema of the tongue, constipation, gastroparesis, pseudo intestinal obstruction, achalasia, mesenteric sclerosis, neurogenic bladder with urinary incontinence, orthostatic edema, discoid lupus erythematosus, bullous pemphigoid, chronic pruritus without skin lesions, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, frozen shoulder syndrome, aromatase induced arthralgia syndrome, autoimmune hepatitis, backaches, sciatica, Mitochondrial Encephalopathy, Lactic-Acid Syndrome (MELAS), multiple sclerosis, post-herpetic neuropathy, hereditary spastic paraplegia [16,17].

Finally, the world is heading in the right direction by trying to restrict the use of addictive opioids unless absolutely necessary. But what is left? Are we replacing one addictive drug with another? Forty-five years of experience with a great many patients, and no one has ever been addicted to dextroamphetamine in the dosages used for these patients while using it to help correct infertility, prevent miscarriage or various treatment refractory medical conditions. They frequently abruptly stop dextroamphetamine without any withdrawal symptoms, especially in infertility patients completing their first trimester! In fact, switching to dextroamphetamine in some people suffering from pain but finding hardly any relief from high dosage of the combination of oxycodone, oxycontin, and fentanyl had almost complete resolution of pain with dextroamphetamines, and thus completely stop all opiates, such as a 45 year old ex-marine who was suffering from multifocal pain resulting from multiple bone fractures after being severely wounded from an improvised explosive device or as in a man dying from severe chronic pancreatitis [17,18].

Dextroamphetamine sulfate has completely corrected severe abdominal pain and diarrhea in a patient with Crohn's disease who suffered despite extremely expensive tumor necrosis alfa suppressing drugs where her specialist advised a total colectomy, yet shortly after exclusive treatment with very inexpensive dextroamphetamines. Her pain and diarrhea resolved. Despite superior relief of symptoms, and marked reduction in cost, dextroamphetamine does not give the patient a significant increased risk of subsequently developing cancer or a serious infection in contrast to taking the tumor necrosis alfa-suppressing drugs!

There is a new push in the United States headed by people e.g., Mark Cuban and possibly the new administration of the United States to promote generic drugs to try to stop the healthcare crisis related to the huge cost of brand-named drugs. Hopefully they will help to also remove the unwarranted label of amphetamines as class II drugs. Another dopaminergic drug, cabergoline, has also been found to be effective in relieving pain, but side effects preclude its ability to be as effective as amphetamines because of limitation in raising the dosage sufficiently [19,20].

There is no evidence to my knowledge that dextroamphetamine can thwart the progression of cancer though it can alleviate some of the suffering from it [21,22]. However, there is another extremely well tolerated drug that provides marked palliation and longevity of survival even in patients who have extremely advanced cancer with no other treatment options [23].There is evidence that most if not all cancers, especially, but not necessarily reaching the stage of rapid proliferation and metastasis develop the ability to metastasize by producing a membrane progesterone induced immunomodulatory protein called the progesterone induced blocking factor (PIBF) (similar to the fetal placental unit) to allow rapid proliferation of cells, invasion into normal tissue, and evasion of immune surveillance [24-26].This drug named mifepristone seems to be extremely effective even in the cancers with the worst prognosis [27,28].

We have observed that most oncologists do not offer this innocuous therapy, even when apprised of the multiple publications showing its efficacy, and instead frequently advise patients to enter into unproven clinical trials [29,30].

At present oncologists are proud that patients with stage IV non-small cell lung cancer (NSCLC) following treatment with the new check point inhibitors e.g., nivolumab and pembrolizumab or tyrosine kinara inhibitors e.g., Osimertinib for NSCLC positive for the EGFR mutation, are demonstrating a 15% 5-year survival [31]. The research presentation that we are giving at the 2025 American Association for Cancer Research is showing for stage IV NSCLC (2/3 of patients) and SCLC (1/3 of patients) not starting mifepristone until progressing after the check-point inhibitor or tyrosine kinara inhibitor have failed are showing a high quality 67% 5 year sur-

vival, and usually death was unrelated to the cancer! Most patients with stage IV SCLC are usually dead within 6 months and hardly anyone survives 5 years [28,31].

In India and China mifepristone costs 50 cents to one dollar a pill but is $42 in the United States. Thus, treatment on a daily dosage of 200mg mifepristone taken orally would cost a patient $15,000 per year out of pocket since it is not approved for treating cancer. In fact, its on-label use to terminate pregnancies has for many years influenced lawmakers and politicians to require a compassionate use investigator new drug application from the United States Food and Drug Administration before it could be prescribed for patients with cancer. To obtain its use for women recently the FDA has lifted that requirement, but it is required that the drug must be sold directly from the manufacturer to the doctor, not the pharmacy or to the patient directly.

Though the price at present in the United States is still far less than the cost of most anti-cancer drugs, the fact that it is a generic drug, its cost could be markedly reduced, and thus be available to all patients even those whose finances preclude obtaining it at the present. Despite multiple publications extolling the benefit of mifepristone for cancer, most oncologists do not seem interested even when there are no more treatment options. Instead of mifepristone they seem to prefer referrals to hospice. Thus, we have recently suggested that this type of immunoendocrine therapy might be better used by endocrinologists who may be more willing to prescribe it related to their familiarity with the drug as progesterone receptor modulator [32].

Unfortunately, those oncologists showing some interest in the endocrine aspects of oncology are evaluating treatment with progesterone receptors antagonists, but they are largely evaluating the wrong type of cancers, i.e., cancers that are positive for the nuclear progesterone receptor e.g., breast, ovarian, and endometrial cancer. However, the nuclear progesterone receptor is protective against cancer and thus progesterone receptor antagonists are best suited for the large majority of cancers that are devoid of the nuclear progesterone receptor, or breast cancers, and endometrial cancers that are negative for the progesterone receptor (e.g., triple negative breast cancer or these cancers that have become more aggressive which is associated with the loss of the nuclear progesterone receptor [33].

Progesterone receptor antagonists probably could be used much earlier than when the cancer becomes metastatic, especially in those cancers devoid of the nuclear progesterone receptor. An example of early use is a man who is now 79 who was given permission to be treated with mifepristone rather than remove both his kidneys related to multifocal renal cell carcinoma. No surgery was performed on his left kidney which had the presence of 3 malignant lesions. He had a right laparoscopic hemi-nephrectomy removing a single larger lesion in his right kidney. He is now 25 years since starting treatment [34].

These are potential ways to make a better progesterone receptor antagonist that also targets another immunomodulatory protein used both by the fetal placental unit and cancer called the progesterone receptor membrane component protein [35]. However, for some reason pharmaceutical companies have not shown much interest.

Thus, the study of the immunology of pregnancy has led to the discovery of 2 very effective, non-toxic, oral drug therapies that can treat the majority of chronic illnesses. Hopefully, the publication of opinions e.g., the present one, will be read and evoke interest in the right scientists, clinicians, entrepreneurs, or politicians to promote widespread evaluation and hopefully confirmation of the tremendous beneficial effects of these 2 drug therapies. Widespread use could markedly reduce the cost of healthcare while at the same time alleviate suffering and extend life of so many patients whose finances and type of insurance coverage prevents them from receiving treatment at the present time by extremely expensive (yet possibly less effective) brand-named drugs available on the pharmaceutical market.

Acknowledgement

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Conflict of Interest

None.

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